Severe hypertriglyceridemia: Causes and treatment

Supervisors: Kjetil Retterstøl, Per Ole Iversen

Ingvild Veseth

Master thesis in clinical nutrition, Department of Nutrition

UNIVERSITY OF OSLO

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Abbreviations

The following abbreviations have been used:

ALAT	Alanine aminotransferase
Apo	Apolipoprotein
ASAT	Aspartate aminotransferase
BMI	Body mass index
BP	Blood pressure
CE	Cholesterol ester
CETP	Cholesterol ester transfer protein
CHD	Coronary heart disease
CI	Confidence interval
CK	Creatinine kinase
CM	Chylomicrons
CRP	C-reactive protein
CVD	Cardiovascular disease
FT_4	Free thyroxin
HbA1c	Glycosylated haemoglobin A
HDL	High-density lipoproteins
HL	Hepatic lipase
IDL	Intermediate-density lipoproteins

LCAT	Lecithin-cholesterol acyl transferase
LDL	Low-density lipoproteins
LDLR	Low-density lipoprotein receptors
Lp (a)	Lipoprotein little a
LPL	Lipoprotein lipase
PPAR	Peroxisome proliferator-activated receptors
SD	Standard deviation
TG	Triglycerides
TSH	Thyroidea-stimulating hormone
VLDL	Very-low-density lipoproteins
WHO	World Health Organisation

Norsk sammendrag

Bakgrunn: Hypertriglyseridemi er en tilstand der fastende triglyserid (TG) verdier er forhøyet. Flere arvelige og ervervede faktorer kan føre til hypertriglyseridemi. Veldig høye TG verdier har vist å øke risikoen for hjerte- og karsykdom og akutt pankreatitt. Kombinasjonen av livsstilsendringer og medisinsk behandling er ofte nødvendig i behandlingen av pasienter med høye TG verdier.

Mål: Denne studien ønsker å kartlegge ulike primære og sekundære årsaker til hypertriglyseridemi, i tillegg til å lage en beskrivelse av pasienter med alvorlig hypertriglyseridemi. Studien vil også beskrive hva slags behandling deltagerne fikk på Lipidklinikken, og effekten av denne behandlingen. I tillegg, forekomsten av hjerte- og karsykdom og akutt pankreatitt i denne studiepopulasjonen vil bli anslått.

Studiepopulasjon og metode: Studien inkluderte 65 individer som var henvist til Lipidklinikken, Oslo Universitetssykehus-Rikshospitalet, i perioden 2002-2007. Alle hadde en målt fastende TG verdi ≥10 mmol/L i løpet av behandlingen på Lipidklinikken. Journalene deres ble brukt som en kilde til informasjon.

Resultater: Av alle deltagerne hadde 28 pasienter en registrert primær diagnose som kunne forklare hyperlipidemien deres. Resten av pasientene hadde minst én sekundær diagnose i tillegg til hyperlipidemien deres. De fleste deltagerne brukte en eller flere lipidsenkende medisiner. TG og total-kolesterol verdiene var signifikant reduserte etter start av behandling. Totalt 19 deltagere hadde en medisinsk historie med hjerte- og karsykdom og 11 pasienter hadde opplevd pankreatitt.

Konklusjon: Denne pasientgruppen er i en høy grad affisert av morbiditet. Medisinsk behandling, antakelig i kombinasjon med livsstilsendringer, førte til en bedring i deres lipidprofil.

English summary

Background: Hypertriglyceridemia refers to a condition where fasting plasma triglyceride (TG) level is elevated. Several inherited and acquired factors can lead to hypertriglyceridemia. Very high TG values have shown to increase the risk for coronary heart disease (CHD) and acute pancreatitis. The combination of lifestyle changes and medication are often necessary in the treatment of patients with high TG levels.

Aims: The present study aims to map different primary and secondary causes of hypertriglyceridemia, in addition to make a description of patients with severe hypertriglyceridemia. The study will also describe what kind of treatment the participants received at the Lipid Clinic, and the effect of this treatment. In addition, the prevalence of CHD and acute pancreatitis in the study population will be estimated.

Study population and method: The study included 65 individuals who were referred to the Lipid Clinic, Oslo University Hospital-Rikshospitalet, in the period 2002-2007. They all had a measured fasting TG level ≥10 mmol/L at some point during their treatment at the Lipid Clinic. Their medical journals were used as a source for information

Results: Of all the participants, 28 patients had a registered primary diagnosis that could explain their hyperlipidemia. The remaining patients had at least one secondary diagnosis in addition to their hyperlipidemia. Most of the participants used one or several lipid-lowering medications. Their TG and total-cholesterol levels were significantly reduced after start of treatment. In total, 19 participants had a medical history of CHD and 11 patients had experienced pancreatitis.

Conclusion: This patient group is in a high degree affected by morbidity. Medical treatment, probably in combination with lifestyle alterations, led to an improvement in their lipid profile.

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1. Background

1.1 Hypertriglyceridemia

Triglycerides (TG) are fatty substances which can be found in blood and in food that contain fat. In everyday language TG are what we call fat. The greatest sources for fat in the Norwegian diet are margarine and fat used in cooking, milk and dairy products, meat and meat products (1). Hypertriglyceridemia refers to a condition where fasting plasma TG level is elevated. Hyperlipidemia is a term which includes all forms of elevated blood lipids, while combined hyperlipidemia is a condition where both the TG and cholesterol levels are elevated. Factors contributing to elevated TG levels include overweight, pregnancy, excess alcohol intake, several diseases, drugs and genetic disorders (2). According to the World Health Organisation (WHO), 1.6 billion adults were overweight in 2005. WHO further projects that approximately 2.3 billion adults will be overweight by 2015 (3). With this increasing prevalence of overweight in the population, and its associated complications, one might expect that hypertriglyceridemia will become more customary, as well as complications due to this condition. Very high TG increase the risk not only for coronary heart disease, but also for acute pancreatitis (2;4).

1.1.1 Clinical manifestations

Hypertriglyceridemia may manifest clinically as eruptive cutaneous xanthomas, which appear as yellow eruptions 2-5 mm in diameter, often with erytematous areolae (figure 1). They will often appear in clusters on the skin of the trunk, buttocks or extremities. This manifestation is often associated with conditions with markedly elevated plasma chylomicrons in cases of familial chylomicronemia, or primary mixed dyslipidemia. Persons with hypertriglyceridemia have lipemic plasma. Lipemic plasma is blurred and not clear and transparent as ordinary plasma appears. When the plasma TG concentration exceeds 35 mmol/L one might see a milky appearance of the retinal vessels and a pink retina. This manifestation is called lipemia retinalis. Tuberous xanthomas, often moveable and nontender, may appear on

extensor surfaces in patients with type III hyperlipoproteinemia. In addition, hypertriglyceridemia might cause xanthoma striata palmaris which appear as yellowish deposits within palmar creases. These skin lesions are only seen in patients with type III hyperlipoproteinemia (5).

Figure 1. Clinical manifestations of hypertriglyceridemia (5).

A: Eruptive cutaneous xanthomas (here on a patient's knee). B: Lipemic plasma. C: Lipemia retinalis. D: Tuberous xanthomas. E: Xanthoma striata palmaris

1.1.2 Epidemiology of hypertriglyceridemia

Various expert panels have made statements and recommendations during the last decades. The National Cholesterol Education Program in USA has divided fasting TG values into 4 different strata: normal (<1.69 mmol/L), borderline-high (1.69-2.25 mmol/L), high (2.26 and 5.63 mmol/L) and very-high (>5.64 mmol/L) (6). TG values >10 mmol/L are considered as severely elevated (2). It is estimated that 2-3 % of the

American population have very high TG levels. However, less than 1 out of 5000 persons have TG values above 10 mmol/L (4). Results from a study conducted in Norway in the period 1985-1999 among persons aged 40-42 years, showed that 3.9 % of the male and 0.57 % of the female study population had TG levels >5 mmol/L. In addition, 0.25 % men and 0.037 % women had TG levels >10 mmol/L. (Anja Schou Lindman, National Public Health Institution, personal communication).

1.2 Lipoprotein metabolism

Fats are not soluble in water and are therefore transported in the blood in lipoprotein particles (7). Lipoproteins are a family of particles that can be divided into five classes by ultracentrifugation, from the least dense and largest to the most dense and smallest. These five classes are called chylomicrons (CM), very-low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), low-density lipoproteins (LDL), and high-density lipoproteins (HDL). The lipoproteins appear to function as an efficient mechanism for the transport of their core components, TG and cholesterol ester (CE), in the circulation (figure 2). In addition to these core components, they consist of an outer surface monolayer of phospholipids and free cholesterol, and each lipoprotein particle contains one or more protein molecules, called apolipoproteins (apo) (8). The CM and VLDL particles are often referred to as the TG-rich lipoproteins, and are mainly concerned with delivery of TG to tissues, mainly muscle and adipose tissue, for storage and use. LDL and HDL particles are more involved in the cholesterol transport to and from cells. IDL particles are catabolic products of CM and VLDL particles (9). More characteristics of the major lipoprotein classes are listed in table 1.

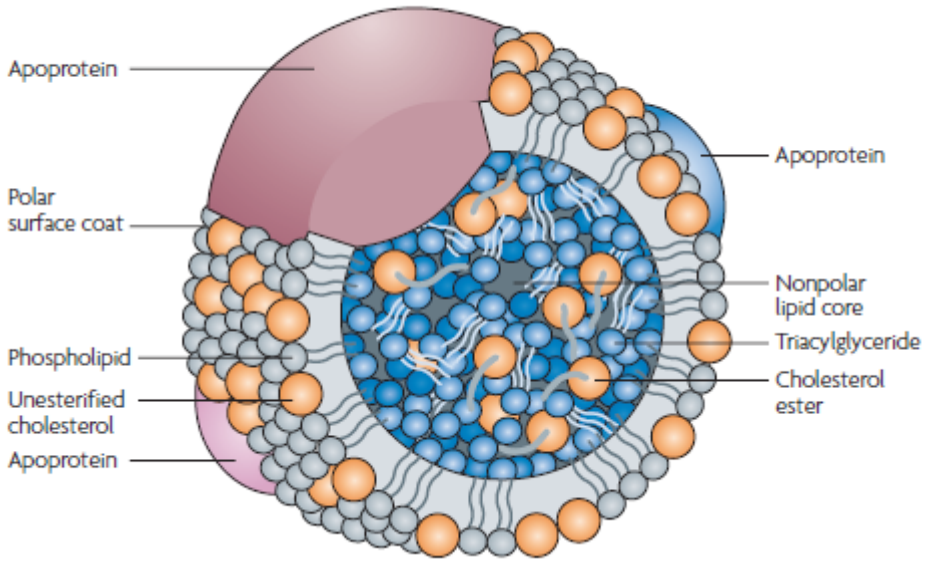

Figure 2. Schematic illustration of a lipoprotein particle (10).

Table 1. Characteristics and functions of the plasma lipoproteins (7;11).

	CM	VLDL	IDL	LDL	HDL
Density g/ml	<0.950	0.950- 1.006	1.006- 1.019	1.019-1.063	1.063-1.210
Origin	Intestine	Liver	Plasma (from VLDL)	Plasma (from IDL)	Liver, intestine
Physiologic role	Transport of exogenous (dietary) TG	Transport of endogenous TG	LDL precursor	Cholesterol transport	Reverse cholesterol transport
Half-life	6 min	1-12 hours	≈24 hours	60 hours	120 hours
Composition (%)					
-TG	90	60	40	10	5
-Cholesterol	5	10	30	50	20
-Phospholipid	3	18	20	15	25
-Protein	2	10	10	25	50
Apolipoproteins	A-I, IV B-48 C-I, II, III	B-100 C-I, II, III E	B-100 E	B-100	A-I, II

1.2.1 Intestinal fatty acid absorption and chylomicrons

CM particles are TG-rich lipoproteins which are derived from dietary fat from the gut (8). After a meal, over 90 % of the TG concentration in plasma originate from the intestine and are found in circulating CM particles (5). The dietary intake of TG will normally account for the overall majority of TG input. Because of several meals per day, there will be a wide fluctuation of plasma TG levels throughout the day. Plasma TG levels should be determined after overnight fasting for comparison with normal values established in fasting normal populations (8).

The metabolism of CM particles is often called the exogenous pathway of lipoprotein metabolism since it is the pathway for transporting fat which originates from our diet (9). TG from the diet are hydrolyzed into monoglycerides and free fatty acids by the aid of several lipases (mainly pancreas lipase). Together with bile acids the lipids make micellar configurations, and are then absorbed into intestinal cells probably by passive diffusion (7). If the fatty acids constitute ten carbon atoms or less they are absorbed as free fatty acids and pass into the portal circulation where they are carried directly to the liver. Long chain fatty acids are mainly absorbed as monoglycerides and are re-esterified into TG in the intestinal cells. The TG are assembled together with apo B-48 and apo A`s to form CM particles which pass into the thoracic duct. In the circulation the CM particles receive apo C-II from HDL particles (12). Following hydrolysis of TG in CM particles, by the action of an enzyme called lipoprotein lipase (LPL), apo C-II is released and again picked up by HDL particles (8). The CM particles have now lost some of their TG core as well as some unesterified cholesterol, phospholipids and apolipoproteins from their surface. The particles have become enriched in cholesterol ester and are called CM remnants. These remnants are transported to the liver where they are taken up by the cells via receptors, for instance by aid of the LDL-receptor related protein (9). The remnants may also be taken up by macrophages and consequently cause cholesteryl ester accumulation in these cells. This has been linked to the development of atherosclerosis (13). Figure 3 gives an overview of the lipoprotein metabolism.

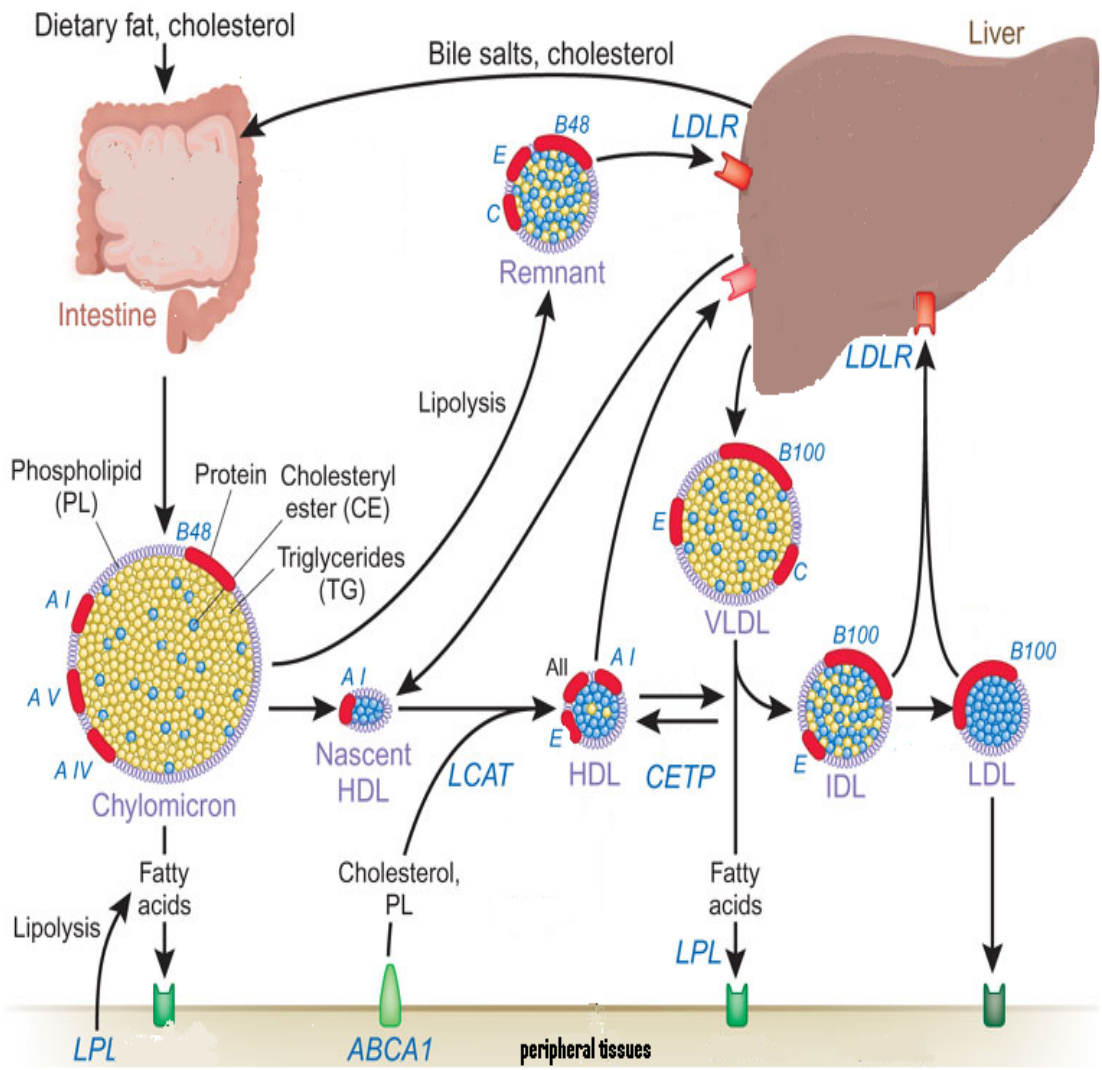

Figure 3. Human lipoprotein metabolism (modified picture) (14) .

1.2.2 Very-low-density lipoproteins

The VLDL metabolism is called the endogenous pathway of lipoprotein metabolism, because TG- rich VLDL particles are synthesized and secreted from the liver (9). Endogenous TG predominate in the circulation during fasting (5). LPL will hydrolyse TG in VLDL particles. This contributes to the delivery of TG to extrahepatic tissues, in addition to surface material from VLDL to other particles, mainly HDL (8). The relatively cholesterol ester-enriched particles, which result after several cycles of lipolysis by LPL, may be taken up directly by a receptor in the liver and other tissues. This receptor is called the LDL receptor (LDLR) and binds a region in apo B-100 and

in apo E. Otherwise, the particles may remain in the circulation, and by the action of LPL and hepatic lipase (HL) they gradually continue to loose their contents of TG. Eventually, the resulting particles consist of a core enriched in cholesterol ester. They have lost all their surface components, except for apo B-100 and a layer of phospholipids and free cholesterol, and they have now become LDL particles (9).

1.2.3 Low-density lipoproteins

LDL is a cholesterol-rich particle which is removed from plasma by hepatic and extrahepatic tissues. LDL appears to be recognized by a specific high-affinity binding site present on the cell surface of tissues, namely the LDLR (13). Although expressed in most nucleated cells, the LDLR and the LDL uptake is particularly active in the liver (9). The bound lipoprotein is internalized by the cell in an endocytotic vesicle. The protein moiety of LDL is degraded, and the cholesterol esters, TG and phospholipids are hydrolyzed (13). The cellular cholesterol content is regulated by the SCAP-SREBP2 system. When the cellular cholesterol level is low, the cells up-regulate the cholesterol synthesis and the expression of LDLR, and when the cholesterol content is high the opposite will happen (15). Scavenger receptors might also take up LDL particles. Different cells express these receptors, particularly macrophages, which are not subject for down-regulation like the LDLR (9).

1.2.4 High-density lipoproteins

HDL particles are secreted form the liver and intestine as pre-β HDL, and originally they contain only apo A-1 associated with some phospholipids. These particles acquire cholesterol by the interaction with other cells. In addition, they acquire surface material released during lipolysis of TG-rich lipoproteins. In this way the nascent HDL particles mature into cholesterol-rich particles. The metabolism of HDL and VLDL particles are closely linked. The HDL-cholesterol concentration is usually low when the TG concentration is high (9).

There is a constant recycling of HDL particles between smaller, cholesterol-depleted (HDL_3), and larger cholesterol- rich types (HDL_2). The transport of cholesterol from

extrahepatic tissues and back to the liver is dependent on a membrane-associated protein, ABC-A1, and an enzyme that esterifies cholesterol, lecithin-cholesterol acyl transferase (LCAT). The HDL particles deliver their cholesterol to the hepatocytes via scavenger receptor-BI without itself being internalised. An alternative route is the transfer of cholesterol in HDL particles via the action of cholesterol ester transfer protein (CETP) to TG-rich particles (9).

1.2.5 Lipoprotein lipase

LPL is found in different tissues, particularly adipose tissue, skeletal muscle and heart muscle, where it is attached to endothelial cells of capillaries (9). It is synthesized within the cells of the tissue and will following secretion and transport to the capillary endothelial cell hydrolyse the TG in TG-rich lipoproteins. Released fatty acids are used by the muscle cells for metabolism and by the adipose tissue for re-synthesis and storage of TG. The enzyme is insulin sensitive, and a rise in insulin secretion following a meal will have a stimulating effect (8).

1.2.6 Hepatic lipase

HL is an enzyme present in the liver, which can hydrolyse both TG and cholesterol esters (9). However, HL prefers TG in remnant lipoproteins, in contrast to LPL which appears to prefer newly synthesized lipoprotein TG as substrate (8).

1.2.7 Apolipoproteins

There are nine major apolipoproteins involved in the lipoprotein metabolism: A-I, A-II, A-IV, B (48 and 100), C-I, C-II, C-III, D and E. Apo A-I is an activator of LCAT. Apo B-48 is produced in the intestinal cells and is found in CM particles. Apo B-100 is produced in the liver and incorporated into VLDL particles. LDL will also contain apo B-100. There is only one molecule of apo B present per particle, and they function as a ligand for receptors. Apo C-II is an activator of LPL (9), while apo C-I and C-III might inhibit the same enzyme. TG concentrations have shown to be 49 % higher in subjects with high Apo C-I and Apo C-III levels compared to those with low Apo C-I and Apo C-III levels (16). Apo E exists mainly in three isoforms: E2,

E3, E4, and an individual carries two alleles for this protein. This apolipoprotein is found on CM, VLDL and HDL particles, and serves as a ligand for receptors (9).

1.3 Primary hypertriglyceridemia

Hypertriglyceridemia can be divided into primary (inherited) and secondary (acquired) types. It can be difficult to distinguish between them because primary hyperlipidemias often are affected by other factors like diet, lifestyle and different medical conditions (2).

1.3.1 Classification

There are several ways to classify the different lipid disorders. The Fredrickson system of hyperlipidemia phenotypes is one of them, and has also been used in the present study (table 2). Five of the 6 Fredrickson types contain elevated TG levels as an essential diagnostic future (17). Another classification system is the International Classification of Diseases (ICD-10) (18). This system is also widely used to distinguish between different disorders of the lipoprotein metabolism.

1.3.2 Type I hyperlipoproteinemia

Type I hyperlipoproteinemia in the Fredrickson system, also known as familial chylomicronemia, is characterized by severe fasting hypertriglyceridemia and massive accumulation of CM particles in plasma. The condition causes an initial manifestation during childhood (19). Chylomicronemia accompanied by eruptive xanthoma, lipemia retinalis and/or abdominal symptoms is referred to as the chylomicronemia syndrome, and can cause acute pancreatitis (20).

Patients with the chylomicronemia syndrome usually have fasting TG levels greater than 10 mmol/L and the plasma TG concentration may even reach 100 mmol/L. Still, this condition does not seem to be associated with premature atherosclerosis (19). An explanation might be that the lipoprotein particles will be very large at such extreme TG levels, and consequently not able to penetrate the intima of arteries (21). However, some studies have identified peripheral and coronary atherosclerosis in

patients with familial chylomicronemia before the age of 55 years (22). CM particles are usually present in plasma after 12 hours fasting in subjects with chylomicronemia syndrome. Chylomicronemia is easily detected in a plasma sample because of the creamy appearance. The most common underlying molecular defect leading to familial chylomicronemia is LPL deficiency. This disorder is inherited as an autosomal recessive trait with a frequency in the general population of about 1 per 1 million persons. The syndrome can also be caused by a familial deficiency of apo C-II. This rare genetic disorder is also inherited as an autosomal recessive trait. The absence of apo C-II results in a functional deficiency of LPL. Patients with LPL deficiency present at an earlier age with more severe hypertriglyceridemia, and lower tolerance to dietary fat in comparison to patients with deficiency of apo C-II (19). A familial circulating plasma inhibitor of LPL might also lead to elevated CM levels in the plasma. Unlike the patients with LPL or apo C-II deficiency, this condition seems to be inherited as an autosomal dominant trait (23).

1.3.3 Type IIa hyperlipoproteinemia

This disorder is more known as familial hypercholesterolemia (FH), and is an autosomal dominant disorder. The condition is characterized by a high plasma concentration of LDL-cholesterol due to defects in the LDLR gene, tendon xanthomas and increased risk of premature coronary heart disease (CHD). In addition, some patients can have elevated levels of TG as a result of the interaction with other genes or environmental factors. However, the TG levels are usually in the normal range (24).

1.3.4 Type IIb hyperlipoproteinemia

Type IIb in the Fredrickson system, also called familial combined hyperlipidemia, is an autosomal dominant disorder. Still, no single gene has been identified as a causative factor (25). Type IIb hyperlipoproteinemia is considered as one of the most common genetic hyperlipidemias in the general population, with an estimated prevalence of 0.5-2.0 % (26).

Type IIb hyperlipoproteinemia is characterized by: (1) an increase in the cholesterol and/or the TG levels in at least two members of the same family, (2) intra-individual and intra-familial variability of the lipid phenotype, and (3) an increased risk of premature CHD (26). The lipid abnormalities in type IIb hyperlipoproteinemia are usually an increase of plasma TG and/or plasma cholesterol levels, elevated apo B, and small dense LDL particles. Despite a reduction in plasma TG concentrations, small dense LDL particles have been shown to persist in patients with this lipid disorder (27). Reduced levels of HDL-cholesterol are also a frequent finding in patients with type IIb hyperlipoproteinemia (26). The increase in circulating apo B and TG levels have been shown to be a result of an increased secretion of VLDL particles (28). However, other studies indicate that the causative factor is a reduced removal rate of TG from the plasma, due to a defective activity in enzymes like LPL (29).

1.3.5 Type III hyperlipoproteinemia

Type III hyperlipoproteinemia is also known as familial dysbetalipoproteinemia. This lipid disorder has a population prevalence of 1-2 in 20000 (5). The primary molecular cause of this lipid disorder is the presence of apo E2. Apo E2 differs from the most common isoform of apo E, namely apo E3, by a single amino acid substitution (cystein for arginine at residue 158). The disorder is associated with a recessive inheritance (30). Apo E plays a central role in the lipid metabolism by serving as a ligand for the binding of lipoproteins to lipoprotein receptors. The apo E2 variant is defective in binding to the LDLR (31). The disorder is characterized by elevated plasma cholesterol and fasting TG levels, usually to approximately equal levels. Accumulation of CM remnants and VLDL remnants, known collectively as β-VLDL, are the diagnostic hallmark of the disease. These lipoproteins are enriched with cholesterol, TG and apo E (30).

Development of overt hyperlipidemia requires homozygosity for apo E2. Interestingly, less than 10 % of apo E2 homozygotes actually develop the hyperlipidemia. Additional genetic, hormonal or environmental factors are required

to give expression to the hyperlipidemia (30). In an analysis of 64 patients with type III hyperlipoproteinemia, 72 % were obese (BMI >25 kg/m^2) and 14 % had diabetes mellitus, making these two conditions the most common additional factors in patients with familial dysbetalipoproteinemia (32). The risk of coronary artery disease has been found to be strikingly elevated in patients with type III hyperlipdemia, also after adjusting for other risk factors (33). In one study, 39 % of the patients with type III hyperlipidemia had atherosclerotic vascular disease (32). Peripheral vascular disease was more pronounced than both coronary artery disease and cerebrovascular disease.

1.3.6 Type IV hyperlipoproteinemia

Hyperlipoproteinemia type IV in the Fredrickson system is also known as familial hypertriglyceridemia. The condition is diagnosed according to the following criteria: (1) the patient has isolated hypertriglyceridemia, (2) isolated hypertriglyceridemia is also present in other family members, and (3) none of the family members suffer from any other dyslipoproteinemia. The condition is usually diagnosed in adults, and the inheritance is autosomal dominant (34). The disorder has an estimated prevalence of 1 % among adults of European descent (35). Type IV hyperlipoproteinemia is characterized by an elevation of VLDL particles, and the patients usually present with moderately elevated levels of TG and low levels of HDL-cholesterol. The molecular basis of this disorder is not solved. Familial hypertriglyceridemia is likely to be polygenic, requiring a secondary factor for expression. The condition is associated with increased CHD risk (17).

1.3.7 Type V hyperlipoproteinemia

Type V in the Fredrickson system, also called primary mixed hyperlipoproteinemia, is usually characterized by elevated levels of both CM and VLDL particles (17). There is a pathologic presence of CM particles after a 12-14 hours period of fasting. The fasting TG measurements are typically >10 mmol/L. This condition usually manifests in adulthood, often together with other secondary factors. The population prevalence is about 1:1000 (5). The basic defects are still unknown. Patients with this primary hyperlipidemia have increased risk of coronary disease (34).

Table 2. Primary types of hypertriglyceridemia.

Dyslipidemia	Fredrickson phenotype	ICD-10	Mechanism	Lipoprotein abnormality
Familial chylomicronemia	Type I	E78.3	LPL deficiency/ apo C-II deficiency	↑ CM particles
Familial hypercholesterolemia	Type IIa	E78.0	Defects in the LDLR gene	↑ LDL particles
Familial combined hyperlipidemia	Type IIB	E78.4	Basis unknown	↑ LDL and VLDL particles
Familial dysbetalipoproteinemia	Type III	E78.2	Homozygous for apo E2	↑ CM and VLDL remnants
Familial hypertriglyceridemia	Type IV	E78.1	Basis unknown	↑ VLDL particles
Primary mixed hyperlipidemia	Type V	E78.3	Basis unknown	↑ CM and VLDL particles

1.4 Secondary hypertriglyceridemia

Secondary hypertriglyceridemia is a condition caused by another primary disorder which has hypertriglyceridemia as a complication (35). Patients with hypertriglyceridemia usually have other lipid disorders as well, and they often have at least one contributing secondary factor (2). Those who develop secondary hypertriglyceridemia might have an underlying inherited defect which makes them susceptible for developing a lipid disorder (5). Table 3 gives an overview over different conditions that might lead to hypertriglyceridemia.

1.4.1 Type 2 diabetes and insulin resistance

Impairment in the ability of insulin to stimulate glucose uptake underlies type 2 diabetes. In individuals who are insulin resistant, but have not yet developed type 2 diabetes, hyperinsulinemia can be associated with other metabolic abnormalities, and together they compose the metabolic syndrome (5). Mild hypertriglyceridemia, with a low concentration of HDL-cholesterol, is a classic feature of insulin resistance and is a characteristic lipid profile in type 2 diabetes (36). In addition, the hypertriglyceridemia in diabetic patients is also associated with a raised concentration

of small, dense LDL particles in the plasma and a greater postprandial CM response (37).

Insulin is an important hormone for the maintenance of normal adipose tissue LPL activity. Untreated diabetic patients appear to have a lower level of adipose tissue LPL, and this can be an important factor in the development of hypertriglyceridemia in these patients (38). Elevated levels of postprandial free fatty acids in plasma might also be one of the contributing factors that stimulate VLDL production in the liver (39). Together this can cause an elevation of TG in plasma.

1.4.2 Obesity

Obesity, especially central obesity, is often associated with several metabolic abnormalities, for instance hyperinsulinemia. Obese individuals might have up to three times higher postprandial TG levels than non-obese individuals (40). An abnormal postprandial lipid pattern is a trait of abdominal obesity even without fasting hypertriglyceridemia (41).

1.4.3 Nonalcoholic fatty-liver disorder

Excess liver fat has recently been recognized as the hepatic component in the metabolic syndrome. Fatty liver is closely related to other components of the metabolic syndrome, for instance dyslipidemia (42). In a study where two groups of patients were compared, the group with fatty liver showed several features of insulin resistance including fasting hyperinsulinemia, hypertriglyceridemia and low HDL-cholesterol concentration, as compared with the patients without fatty liver (43). The increase in TG concentration is the major component of the dyslipidemia in fatty liver disorders. Studies have shown that this lipid abnormality is a result of increased production of large VLDL particles in the liver (44).

1.4.4 Hypothyroidism

Over 90 % of overtly hypothyroid patients have hyperlipidemia (45). Another study found that 14 % of 303 women with dyslipidemia showed sub-clinical

hypothyroidism, while 4 % had an overt hypothyroidism and 2.6 % were already under hormone replacement therapy (46). This shows that unrecognised hypothyroidism is common among dyslipidemic patients. O`Brien et al investigated the lipid profile of 268 patients with primary hypothyroidism and 27 patients with secondary hypothyroidism (47). Hyperlipidemia was commonly associated with both primary and secondary hypothyroidism. Total/ HDL- cholesterol and LDL/ HDL-cholesterol ratios were increased in both male and female patients, and they decreased with replacement of thyroid hormone. Other studies have shown that total-cholesterol, HDL-cholesterol, TG, Lp (a), apo AI and apo B100 are increased in patients with hypothyroidism (48). These results are not entirely consistent with other studies. Lee et al found no significant differences in the concentration of Lp (a), HDL-cholesterol or apo A-I in persons with hyperthyroidism, hypothyroidism and controls (49). However, they did find that TG levels were significantly higher in patients with hypothyroidism compared to those with hyperthyroidism and healthy controls.

The synthesis of plasma TG are found to be normal in patients with hypothyroidism, but the fractional removal of endogenous and exogenous TG are markedly reduced (50). Studies have shown that patients with overt hypothyroidism have decreased post-heparin plasma LPL activity, in addition to HL activity. LPL activity is usually increased by thyroid hormone, and patients with thyroid dysfunction may therefore develop hypertriglyceridemia as a consequence of changes in the activities of these enzymes (51).

1.4.5 Renal disease

Hyperlipidemia is a hallmark of the nephrotic syndrome. The hyperlipidemia is usually characterized by elevated cholesterol levels, although hypertriglyceridemia may be present as well. One hypothesis is that the hyperlipidemia is a result of an increase in the synthesis of proteins in the liver, including lipoproteins. However, this hypothesis has been rejected in later studies where it has been shown that VLDL apo B100 levels were primarily increased as a consequence of a decrease in fractional

catabolic rate rather than from an increase in absolute synthesis rate (52). In addition, the increase in TG level in nephrotic syndrome has been found to be a result of reduced clearance of TG-rich lipoproteins due to a decrease in the presence of endothelial-bound LPL, which occurs as a consequence of reduced serum albumin concentration, and a defect in VLDL binding to endothelial-bound LPL. The latter defect occurs only in the presence of proteinuria (53).

1.4.6 Alcohol

Studies of chronic alcoholics have shown that both the production and the catabolic rate of VLDL-TG were significantly increased compared to a control group of non-alcoholic men. This accelerated catabolism of VLDL might also be responsible for the elevated level of HDL observed in regular alcohol users (54). Plasma TG concentration might also be within the normal range in some alcohol users because of an adaptive increase in lipolytic activity (5). However, ethanol has usually shown to reduce TG clearance from the plasma, probably due to an inhibition of plasma LPL (55).

Studies have shown that a daily intake of alcohol (average 160 g/day) affects both the concentration and composition of fasting and postprandial plasma lipoproteins (56). On the third day of daily alcohol administration, the average concentration of plasma TG was 68 % higher compared to baseline. Alcohol enhanced the postprandial rise of TG in all lipoprotein fractions. Whether alcohol consumption per se increases TG concentration in patients with established hypertriglyceridemia is more unclear than the role of alcohol consumption on TG levels in normolipidemic individuals. In one study, where the mean TG values were 4 mmol/L and 1 mmol/L for the hypertriglyceridemic and non-hypertriglyceridemic groups respectively, the groups differed in TG response despite similar alcohol feeding (57). The participants were advised to fast for 12 hours before they consumed 30 g ethanol, followed by another 10 hours of fasting. Six hours after the alcohol consumption the TG concentration increased with only 3 % in the hypertriglyceridemic group, and with 53 % in the non-hypertriglyceridemic group. The study concluded that acute alcohol intake alone is

not an important determinant of plasma TG concentration in individuals with hypertriglyceridemia.

1.4.7 Pregnancy

During the third trimester of pregnancy plasma TG levels normally increase between two- and four-fold, while plasma cholesterol levels rise by approximately 50 %. Plasma lipid levels normally rise as a result of estrogen-induced hepatic production of TG-rich lipoproteins (58). In addition, it has been reported of an increase in HL activity and a decrease in LPL activity during pregnancy. The net effect will be an increase in circulating TG in plasma (59). This adaptation in the lipid metabolism might be beneficial and serve as extra energy for the mother, provide steroid hormone precursors for the placenta, and provide cholesterol and essential fatty acids for the fetus (60).

Severe hyperlipidemia is a rare complication of pregnancy (58). Although hyperlipidemic pancreatitis in pregnancy is a rare event, patients with pre-existing abnormalities in the lipid metabolism may develop gestational hyperlipidemic pancreatitis. Fredrickson`s type I, IV and V hyperlipoproteinemias have been most commonly associated with acute pancreatitis in pregnancy (61). The risk of maternal and fetal mortality as a result of gestational pancreatitis is approximately 20 % each (62).

1.4.8 Other medical conditions

Autoimmune disorders, like systemic lupus erythematosis, might lead to an elevation in the plasma TG level (63). Several studies have also found a significant association between hyperuricemia (gout) and hypertriglyceridemia (64). The TG concentration may also be elevated in liver diseases, particularly cholestasis. The circulating lipoproteins can be present in abnormal amounts, in addition to have abnormal compositions (65).

1.4.9 Medications

Different drugs might influence the lipid metabolism and increase the plasma TG concentration. One example is protease inhibitors which have several side-effects like lipodystrophy, insulin resistance and hyperlipidemia (66). The use of diuretics has also been shown to result in increased TG levels (67). In addition, medications like corticosteroids, estrogens and resins have been associated with adverse effects on the TG level (5).

1.4.10 Diet

Based on a typical Western diet, most people consume meals at regular intervals, where each meal contains 20-70 g fat (68). After consumption of a fat-containing meal, circulating TG show an increase after 1 hour, a peak after 2-3 hours and can remain high for 5-7 hours (69). Each meal following breakfast is most likely consumed before the plasma TG level has returned to the baseline value. Thus, humans spend most of their day-time in a postprandial fed state (68).

Different nutrients may contribute to inter-individual variability in the postprandial lipemia (table 4). The amount of energy, the composition of a previous meal and meal frequency can be factors influencing the postprandial lipid response. In addition, postprandial lipemia is influenced by the amount and type of dietary fat, as well as carbohydrates (68). A low dose (15 g) of dietary fat in a meal has been shown not to increase the postprandial TG concentration in CM particles (69). However, intake of meals containing 30 g fat and up to 50 g fat led to a stepwise increase in the postprandial TG concentration in CM particles. In addition, replacement of saturated fatty acids with monounsaturated fatty acids in test meals have shown not to affect the postprandial metabolism of TG-rich lipoproteins (70). However, omega-3 polyunsaturated fatty acids from fish oil lower the postprandial TG response if sufficient amounts are given in the test meal (71).

Clinical studies indicate that diets rich in highly digestible carbohydrates can lead to high levels of fasting plasma TG (72). Parks et al conducted a study where they

compared subjects who were either normolipidemic or hypertriglyceridemic on both a control and a low-fat/high-carbohydrate (LF/HC) diet (73). The study diets differed in their percentage of energy from fat and carbohydrate. In addition, the LF/HC diet contained 50 % more fibre and 89 % less cholesterol than the control diet. The LF/HC diet resulted in a 60 % increase in TG, a 37 % reduction in VLDL-TG clearance and 18 % reduction in whole body fat oxidation, but no significant change in VLDL-apo B-48 or VLDL-TG secretion rates. Fasting de novo lipogenesis was low in both groups regardless of diet. However, other studies have found that a high carbohydrate diet leads to an increase in plasma VLDL-TG due to both an increase in hepatic VLDL-TG secretion rate and a reduced catabolism of VLDL-TG (74). Moreover, the amount and nature of carbohydrates in a meal can alter postprandial lipid metabolism. In one study the addition of glucose to a fatty test meal did not induce significantly alterations in postprandial lipemia, while the addition of sucrose or fructose markedly increased the postprandial triglyceridemia (75).

Studies indicate that soluble viscous fibre might cause a reduction in the secretion of chylomicrons into the circulation, possible because they reduce the rate of digestion of dietary fats, and thereby attenuates the postprandial lipemic response (76). Very little information is available considering the influence of protein intake on postprandial lipid response. However, there is evidence indicating that soy protein might have a TG lowering effect. One study found a significant reduction in the TG level with 13.4 % in men who had eaten a diet with soy protein isolate for 3 weeks (77).

Table 3. Secondary conditions that might lead to hypertriglyceridemia.

Secondary conditions	Lipid abnormality	Proposed mechanism
Type 2 diabetes, insulin resistance, obesity	↑ TG, ↓ HDL-cholesterol, ↑ small dense LDL particles	↑ TG production, ↓ TG removal
Fatty liver	↑ TG, ↓ HDL-cholesterol	↑ VLDL production
Hypothyroidism	↑TG	↓ TG removal
Renal disease	↑ TG, ↑ total-cholesterol	↓ TG removal
Pregnancy	↑ TG, ↑ total-cholesterol	↑ VLDL production and/or ↓ removal
Medications (ex. protease inhibitors)	↑ TG, ↑ total-cholesterol, ↑ LDL-cholesterol	↑ VLDL production and/or ↓ removal
Alcohol	↑ TG	↑ production and ↓ removal of VLDL-TG

Table 4. Dietary factors affecting the TG levels.

Dietary factors	Extent of effect on the postprandial lipemia
Amount of fat	+++ (Dose-dependent: 30-50 g/meal)
Type of fat	+/- (n-3 fatty acids have a lowering effect)
Carbohydrates	++ (Diets rich in highly digestible carbohydrates)
Protein	No/- (Soy protein might have a reducing effect)
Fibre	No/- (Soluble viscous fibre have shown a reducing effect)

+++, very important; ++, important; +, moderate increase; -, moderate reduction; No, no noticeable change

1.5 Medical treatment of hypertriglyceridemia

Four principally different groups of lipid-lowering medications are at the moment approved in Norway: statins, niacin, omega-3 fatty acids (fish oil) and resins (78). However, only the first three of them are the main pharmacologic agents for managing hypertriglyceridemia (79). Fibrates are also a group of lipid-lowering medications, but these are not marketed in Norway, although they are available. These different groups of lipid-lowering medications have somewhat different effects on the lipid levels (table 5).

The treatment strategy for elevated TG depends on the cause of the elevation and its severity. In patients with secondary hypertriglyceridemia it is important to treat the

primary condition first (2). For persons with borderline-high or high TG levels, the primary aim of therapy is to achieve the target goal for LDL-cholesterol (2.6 mmol/L for patients with CHD). For patients with high TG levels, non-HDL-cholesterol (LDL+VLDL-cholesterol) becomes a secondary target of therapy (non-HDL-cholesterol goal: 3.4 mmol/L for patients with CHD) (6). For persons with borderline-high TG levels therapeutic lifestyle changes are often sufficient, in patients with high TG levels, drug therapy should be considered in addition. Statins with TG-lowering properties are first line agents for patients who have not reached their LDL-cholesterol goal. In patients with high TG levels, who have reached their LDL-cholesterol goal, a fibrate, niacin or fish oil can be considered. Some patients might also require a combination therapy to reach their LDL-cholesterol and non-HDL-cholesterol goals. Patients with very-high levels will usually require drug therapy in addition to therapeutic lifestyle changes. Fibrates or niacin is often a first-line choice for these patients (79). The initial aim of therapy in patients with very-high TG levels is to prevent acute pancreatitis through TG lowering (6).

1.5.1 Statins

Atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin and simvastatin constitute a group of medications called statins. Statins inhibit hydroxymethylglutaryl coenzyme A-reductase (HMG-CoA-reductase), the rate limiting enzyme in cholesterol biosynthesis. Inhibition of this enzyme leads to reduced cholesterol synthesis and therefore a reduced hepatic cholesterol content. This results in an increase in the expression of LDL-cholesterol receptors (78). This up-regulation lowers the concentration of TG-rich lipoproteins in plasma because IDL and VLDL remnants are removed from the circulation via these receptors (13). Compared with placebo, atorvastatin has shown to significantly decrease the concentration of total-cholesterol, TG, LDL-cholesterol and VLDL-apo B (80). In addition, the Scandinavian Simvastatin Survival Study (4S) showed that long-term treatment with simvastatin was safe and improved survival in CHD patients (81).

1.5.2 Fibrates

The effect of fibrates is mediated through alterations in the transcription of genes encoding for proteins that control the lipoprotein metabolism. Fibrates activate the nuclear receptors termed the peroxisome proliferator-activated receptors (PPAR), which bind to specific response elements on DNA and alter the transcription rate of target genes. Of the different PPARs, the PPARα form is predominantly expressed in the liver and mediates fibrates action on lipoproteins. The effects of fibrates are: (1) induction of lipoprotein lipolysis due to an induction of LPL expression, (2) induction of hepatic fatty acid uptake and reduction of hepatic TG production, (3) induction of alterations in the plasma LDL composition and structure, which results in the formation of LDL with a higher affinity for the LDLR, and hence increased removal of LDL particles (82).

In patients with type IIa, IIb and type IV hyperlipoproteinemia, fibrates have shown to cause a decrease in both total-cholesterol, LDL-cholesterol, plasma VLDL levels and an increase in HDL-cholesterol (83). In addition, fibrates can lead to an improvement in postprandial lipemia, which is likely due to LPL mediated enhancement of lipolytic hydrolysis (84). Fibrate therapy has been shown to decrease the risk of cardiovascular events in patients with cardiovascular disease (secondary prevention) (85).

1.5.3 Niacin

The primary action of niacin is to inhibit the mobilization of free fatty acids from peripheral tissues, thereby reducing hepatic synthesis of TG and secretion of VLDL particles (86). In pharmacologic doses, niacin reduces the concentration of total-cholesterol, LDL-cholesterol, TG, VLDL, Lp (a), and increases the HDL-cholesterol (87). Concerns over worsening glycemic control have led to discouraging the use of niacin in treatment of patients with diabetes. However, a study of patients with and without diabetes taking lipid-lowering doses of niacin, demonstrated that niacin could be safely used in patients with diabetes without significantly affecting the glycemic control, in addition to exert beneficial effects on the lipid levels (88). Results from the

Coronary Drug Project Study reported that treatment with niacin reduced the rate of nonfatal myocardial infarction and the total 15-year mortality rate with 11 % compared with the placebo group (89).

The use of niacin is limited because of adverse effects including flushing and gastrointestinal symptoms. Three different niacin formulations are currently available: immediate release, extended release and long acting. Almost all patients who use immediate release niacin will experience cutaneous flushing at the start of therapy. The long acting niacin is associated with a lower incidence of flushing. However, gastrointestinal and hepatotoxic side effects are more common and severe with this type of niacin. The use of extended release preparations have shown to result in less flushing and less risk of hepatotoxic effects compared with the two other niacin formulations (90).

1.5.4 Fish oil

Fish oil contains high amounts of the long omega-3 fatty acids termed docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) (79). Fish oils can be used alone in treatment of hypertriglyceridemia, or in combination with for instance statins in the treatment of combined hyperlipidemia (78). The proposed mechanisms for their TG-lowering effect are increased fatty acid oxidation, decreased TG synthesis and/or decreased VLDL cholesterol secretion (91). Patients with hypertriglyceridemia should receive 2-4 g of total EPA/DHA per day. Among different preparations which contain omega-3 fatty acids, Omacor is a highly concentrated form of omega-3-acid ethyl esters, and is also an approved medication for patients with hypertriglyceridemia (79). A systematic review showed that omega-3 fatty acids are effective in lowering TG levels in a dose-dependent manner. The effects of omega-3 fatty acids on other plasma lipids were weaker (92). The GISSI-Prevenzione trial found that treatment with omega-3 fatty acids significantly lowered the risk of primary endpoints (death, nonfatal myocardial infarction and stroke) (93). In contrary, a systematic review showed no strong evidence of reduced risk of total mortality or cardiovascular events in patients treated with omega-3 fatty acids (94).

1.5.5 Other lipid-lowering medications

Resins bind bile acids in the intestine, thereby interrupting the enterohepatic circulation of bile acids. The conversion of cholesterol into bile acids in the liver is therefore increased in addition to the hepatic synthesis of cholesterol. This results in increased secretion of VLDL into the circulation and consequently raised plasma TG levels (86). In contrary, ezetimibe is thought to inhibit a cholesterol transporter in the enterocytes, located within the brush-border membrane of the small intestine. Ezetimibe has been shown to reduce the LDL-cholesterol and TG levels, in addition to cause a modest increase in HDL-cholesterol (95).

Table 5 .The effects of different medications on lipoprotein levels (96).

	Total-cholesterol	LDL-cholesterol	HDL-cholesterol	TG
Statin	↓ 15-60 %	↓ 20-60 %	↑ 3-15 %	↓ 10-40 %
Fibrate	↓ 15 %	↓ 0-15 %	↑ 6-15 %	↓ 20-50 %
Niacin	↓ 25 %	↓ 10-15 %	↑ 15-35 %	↓ 20-50 %
Fish oil	↑ or neutral	↑ or neutral	↑ or neutral	↓ 20-50 %
Ezetimibe	↓ 12 %	↓ 18 %	↑ 1 %	↓ 8 %

1.6 Therapeutic lifestyle changes

Patients with elevated TG levels may benefit from therapeutic lifestyle changes, including change of diet, weight reduction and increased physical activity (6).

1.6.1 Diet

The National Cholesterol Education Program recommends a dietary approach to reduce the overall risk of CHD. Its essential features are a carbohydrate intake representing 50-60 % of total calories, 20-30 g fibre daily, and total fat contributing with 25-35 % of total calories, with reduced intake of saturated fats (<7 % of total calories), and cholesterol (<200 mg/d) (6). At the Lipid Clinic, Oslo University Hospital-Rikshospitalet they have the following dietary guidelines for patients with hyperlipidemia: total fat intake contributing with 25 % of total calories, where

saturated fat and trans-fatty acids should be restricted to <7 % and <1 % of total calories respectively. The intake of monounsaturated fatty acids should represent 10-15 % and polyunsaturated fatty acids 5-10 % (included 1 % from omega-3 fatty acids) of the total calorie intake. The intake of cholesterol should be restricted to <200 mg per day. Protein intake should contribute with 10-20 % of total calories, and carbohydrates 50-60 % of total calories, where maximum 10 % should originate from sugar. In addition, they recommend an intake of 25-35 g fibre, and 2 g plant sterols per day. To achieve these goals the patients referred to the Lipid Clinic will be recommended to eat less fat, and to use plant- and fish-fat as a main source in stead of animal-fat, thus replacing some saturated fat with unsaturated fat in the diet. The patients are also recommended to eat more food rich in fibre, for instance fruit and vegetables, and to eat less of the cholesterol-rich food. Patients who are overweight and/or have elevated TG levels are also recommended to reduce their intake of alcohol and sugary food and drinks (more diet recommendations can be found in appendix 4) (97).

1.6.2 Physical activity

Increased exercise is one of the cornerstones of TG-lowering therapy (6). Aerobic exercise has shown to significantly reduce postprandial lipemia, and significantly increase LPL activity (98). The lipemic response to a meal high in fat and carbohydrate is also related to the intensity of the preceding exercise. In one study, the fasting and postprandial TG concentration was significantly lower after moderate intensity walking compared with the controls. However, the TG concentration was not significantly lower after low intensity walking (99).

1.6.3 Smoking

Axelsen et al found that habitual smokers had a 50 % higher postprandial increase in TG levels than non-smokers (100). However the fasting TG levels were the same in both groups. A different study showed that smokers had a significantly increased postprandial TG response in chylomicrons. In addition, smoking raised apo B-48 postprandially, but apo B-100 concentrations and lipolytic enzymes were similar in

the smoking and in the non-smoking group (101). This might indicate that smoking can lead to a postprandially increase in lipoproteins of intestinal origin. Cessation of smoking will therefore be beneficial in patients with hypertriglyceridemia.

1.7 Cardiovascular disease

Cardiovascular disease (CVD) is a group of disorders that affects the heart and blood vessels. These conditions include CHD, cerebrovascular disease (cerebral infarction, cerebral bleeding), peripheral arterial disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis and pulmonary embolism. CVD is the number one cause of death globally. It is estimated that 17.5 million people died from CVD in 2005, representing 30 % of all global deaths (102).

1.7.1 Vascular risk factors in general

Age, sex, personal and family history of CVD are non-modifiable risk factors for CHD (103). Modifiable factors like unhealthy diet, physical inactivity and tobacco, are responsible for about 80 % of CHD and cerebrovascular disease. The effects of an unhealthy diet and physical inactivity may be raised blood lipids, blood glucose, blood pressure, overweight and obesity (102). For high risk individuals the goal regarding blood lipids is: total-cholesterol <5 mmol/L and LDL-cholesterol <3 mmol/L, while HDL-cholesterol <1 mmol/L and fasting TG >2.0 mmol/L are markers of increased CHD risk (104) .

1.7.2 Elevated triglycerides as a risk factor

Elevated cholesterol levels, in addition to low HDL-cholesterol levels, are regarded as important risk factors for CHD (103). Several studies are now indicating that elevated TG levels might also constitute a significant, independent risk for CVD in men and women in the general population (105). Pelkonen et al found that the relation between TG concentration and cardiovascular death was not linear (106). Increased risk were only seen when TG concentration was >1.7 mmol/L. This discovery makes TG different from other risk variables, like plasma cholesterol

concentration, cigarette smoking and blood pressure which are linearly correlated with disease events. In comparison, the Copenhagen Male Study concluded that the risk of CHD increased with TG levels above 1.1 mmol/L (107). This study followed 2906 men, who were initially free of overt CVD, for eight years. The study population was divided into thirds (three groups) based on their TG level: <1.1 mmol/L, 1.1-1.6 mmol/L and >1.6 mmol/L. They found a clear gradient of risk for CHD with increasing thirds of TG levels. Compared with the lowest third, the risk of CHD was 50 % higher in the middle third and 120 % higher in the highest third after controlling for other major risk factors.

In the Prospective Cardiovascular Munster Study (PROCAM) they analyzed cardiovascular risk factors in nearly 5000 male participants aged 40-65 years in a follow-up period for 8 years (108). Analyses revealed that moderately elevated levels of TG emerged as an independent predictor for the risk of major coronary events (nonfatal myocardial infarction, fatal myocardial infarction, sudden cardiac death). The ranking of the continuous risk factors for predictive value for CHD was: LDL-cholesterol > total-cholesterol > HDL-cholesterol > TG > fasting blood glucose > systolic blood pressure > body mass index.

Blood lipid alterations after a fatty meal may be atherogenic. The Atherosclerosis Risk in Communities Study showed an association between postprandial TG and carotid atherosclerosis defined by intima-media thickness. This finding was independent of fasting lipids and other risk factors in non-obese, white, middle-aged subjects (109). An elevated level of non-fasting TG is a marker for elevated levels of CM and VLDL remnant particles which are able to promote atherosclerosis. These remnant lipoproteins can penetrate into the arterial intima, and get trapped within the subendothelial space (110). Several recent studies have focused on non-fasting TG levels and risk of myocardial infarction. The Copenhagen City Heart Study is a prospective cohort study which included 13956 participants (111). They found that the cumulative incidence of ischemic stroke increased with increasing levels of non-fasting TG. The significant results showed that the hazard ratios for ischemic stroke

in men with non-fasting TG of 3.99-4.98 mmol/L and >4.98 mmol/L were 2.2 and 2.5 respectively, compared to men with non-fasting levels less than 1 mmol/L.

It is not known whether the relation between TG and CHD is primarily direct or indirect. TG-rich lipoproteins, particularly VLDL, may be directly atherogenic, or the hypertriglyceridemia may lead to metabolic consequences which contribute to CVD. These consequences might be an increase in postprandial lipoproteins, large VLDL particles, small and dense LDL particles, a low level of HDL-cholesterol and/or possibly a procoagulant state (112). Not all VLDL particles are atherogenic. It is the elevation of small cholesterol rich VLDL particles that are associated with an increased risk of CHD, while the increase in large TG-enriched VLDL particles is not associated with increased CHD risk (113). In addition, hypertriglyceridemia may enhance thrombogenesis through abnormal alterations in coagulation and fibrinolytic mechanisms (114). It has been reported that higher plasma fibrinogen concentrations and higher factor VII coagulant activity are associated with greater risk of cardiovascular disease (115). The fibrinolytic system is regulated by the balance between the levels of tissue-plasminogen activator (t-PA) and plasminogen activator inhibitor (PAI-1). In one study they found that the plasma levels of both t-PA and PAI-1 were significantly higher in patients with hypertriglyceridemia than in normolipidemic patients, and that PAI-1 levels tend towards normalization in conjunction with TG reduction (114). Others have reported alterations in fibrinolytic activity in patients with hypertriglyceridemia. A study by Hamsten et al showed that the level of t-PAI was positively and significantly correlated with levels of serum TG (116). This study included 71 persons who had suffered a myocardial infarction, and these patients were compared with 50 healthy persons three years after the infarction. They found a low t-PA activity after venous occlusion in the patients, explained by high plasma levels of t-PAI and to some extent impaired release of t-PA from the vessel wall. This data implied that reduced fibrinolytic capacity, due to increased plasma levels of t-PAI, may have a pathogenic importance in myocardial infarction, particularly in patients with hypertriglyceridemia. In addition, another study where they analyzed data from The Atherosclerosis Risk in Communities Study, showed

that plasma TG, LDL-cholesterol, HDL-cholesterol and BMI are positively associated with coagulation factor VII (115). In this study, TG showed the most striking correlation: a 0.8 mmol/L increase in TG concentration resulted in a nearly 10 % increase in factor VII.

1.8 Acute pancreatitis

Acute pancreatitis is a relatively common disorder with increasing incidence and several possible etiologies. The clinically appearance can vary from mild self-limiting symptoms to a deadly disease (117).

1.8.1 Pathophysiology of acute pancreatitis

Acute pancreatitis is probably caused by an unregulated activation of trypsin within the pancreatic acinar cells. This enzyme activation will lead to an autodigestion of the gland and local inflammation. Acute pancreatitis can arise when intracellular protective mechanisms, which shall prevent trypsinogen activation and reduce trypsin activity, are overwhelmed. Examples of such protective mechanisms include the synthesis of trypsin as the inactive enzyme trypsinogen, autolysis of activated trypsin, enzyme compartmentalisation and synthesis of specific trypsin inhibitors. After activation of trypsinogen to trypsin within the acinar cells other enzymes are also activated, for instance elastase and phospholipase A2. Activation of these digestive enzymes leads to pancreatic injury and results in an inflammatory response. This acute inflammatory response itself causes substantial tissue damage (117).

1.8.2 Etiology and epidemiology

The most important risk factors for pancreatitis in adults are gallstone and excessive alcohol use. Other causes of acute pancreatitis are metabolic aberrations, like hypertriglyceridemia, duct obstruction, medications and trauma (118). In a Norwegian study of 376 patients, they found that gallstone was the cause in 58 % of the episodes with acute pancreatitis, alcohol in 13 %, hyperlipidemia in 2.4 %, and 14 % of the cases were idiopathic (119). Another study have found that severe

hypertriglyceridemia was the cause in 7 % of the episodes of acute pancreatitis (120). Hypertriglyceridemia as the causative factor in acute pancreatitis differs between studies, thus indicating that hypertriglyceridemia can be difficult to detect and diagnose as the real causative factor. This might in some cases lead to an underestimation of hyperlipidemic pancreatitis.

The incidence of acute pancreatitis seems to be increasing in European countries, and the incidence and mortality rate are also increasing with age. Differences in both the incidence and the etiology of acute pancreatitis exist between countries (121). It is estimated that 10 to 30 % of those with severe acute pancreatitis will most likely die (118).

1.8.3 Diagnosis of acute pancreatitis

Acute pancreatitis is characterized by the presence of acute and constant pain in the epigastric area. This pain might be associated with nausea and vomiting. Elevated amylase and/or lipase are the diagnostic hallmarks of acute pancreatitis. Amylase concentrations normally rise in the serum within a few hours after onset of symptoms, and return to normal values within 3-5 days (117). In the case of pancreatitis due to hypertriglyceridemia, serum and urinary amylase levels are low and may also be normal in more than 50 % of the patients at the time of admission or at the hospital stay (122). This has been explained by the presence of an inhibitor in the plasma and urine that inhibits the assay (123).

The strongest predictor of hyperlipidemia in a patient with acute pancreatitis is the presence of lipemic plasma. Within 24-48 hours of the onset of acute pancreatitis, TG levels usually fall rapidly as a consequence of fasting. In addition, the therapy with hypocaloric intravenous fluids leads to a decrease in the secretion of VLDL from the liver (122). The plasma TG level might be only slightly elevated or even normal a few days after hospital admission. Therefore it is important to consider chylomicronemia at the time of admission to make a correct conclusion about etiology (120). In addition, family history or preexisting medical conditions and medications known to cause hypertriglyceridemia can contribute to identification of

patients with hypertriglyceridemia-induced pancreatitis (122). Computed Tomography can be done to confirm the diagnosis (117).

1.8.4 Hypertriglyceridemia and acute pancreatitis

Patients with hypertriglyceridemia and pancreatitis usually have a preexisting abnormality in lipoprotein metabolism (122). A plasma TG level >11 mmol/L has shown to be associated with an increased risk of acute pancreatitis in patients with type I, IV or V hyperlipoproteinemia, with an incidence of acute pancreatitis up to 21 % (124). An elevation in TG level (2-10 mmol/L) is common in early phase of acute pancreatitis of any etiology. However, this elevation is more likely to be an epiphenomenon of the pancreatic disease rather than a true causal precipitant. A much more marked hypertriglyceridemia would be needed to trigger an acute pancreatitis (125).

1.8.5 Pathogenesis of hypertriglyceride-induced pancratitis

In TG-induced pancreatitis there are elevated levels of CM particles in the circulation, and these particles are believed to be responsible for the pancreatic inflammation. These large lipoproteins might impair circulatory flow in the capillary beds. This can lead to ischemia in the pancreas and hence disturbs the acinar structure and expose the TG-rich lipoproteins to pancreatic lipase. Hydrolysis of TG in and around the pancreas leads to accumulation of free fatty acids in high concentrations. Unbound free fatty acids are toxic and can produce acinar cell or capillary injury, in addition to activate trypsinogen and with that initiate acute pancreatitis. Subsequently, there will be a release of inflammatory mediators and free radicals and the result might be necrosis, edema and inflammation (122). An animal study which examined the development of pancreatitis due to hyperlipoproteinemia type 1, found that mitochondrial swelling was the dominating early change in the pancreas. Fatty acids are known to induce mitochondrial swelling, and increased concentrations of free fatty acids in the acinar cells might therefore trigger reactions that lead to pancreatitis (126). The inflammatory response may progress beyond the pancreas to a systemic inflammatory response syndrome, multiorgan failure or death (117).

1.9 Current issues

This is the first study to examine the occurrence of conditions associated with severe hypertriglyceridemia in Norway. Since the Norwegian population might differ from those in other countries with respect to occurrence of conditions associated with hypertriglyceridemia, this knowledge is of clinically importance. The characterization of patients with severe hypertriglyceridemia is important since it can enable clinicians to identify patients at risk. In addition, hypertriglyceridemia as a result of secondary conditions might be overlooked and remained untreated. Therefore, it is of clinical significance that conditions which are usually associated with high TG values are well known, so patients can receive an adequate treatment, and achieve a reduced risk of CHD and pancreatitis.

The Lipid Clinic is an out-patient`s clinic at Oslo University Hospital-Rikshospitalet, which receives referrals of patients from all over the country. The clinic gets approximately 700 new-referrals each year, and has an important role in the treatment of patients with hyperlipidemias from all over Norway. It is of interest and importance to evaluate the effect of the treatment at the Lipid Clinic, with reference to clinical measures and blood lipids. Such an evaluation might contribute to better treatment of patients with hypertriglyceridemia in the future.

2. Aims and approach to the problems

The following questions will be answered:

(i) What are the most common primary and secondary causes of severe hypertriglyceridemia in patients receiving treatment at the Lipid Clinic, Oslo University Hospital-Rikshospitalet?

(ii) What kind of treatment have these patients received at the Lipid Clinic?

(iii) How can this population be described with regard to clinical measurements and blood samples before start of treatment at the Lipid Clinic? What alterations have occurred in these clinical parameters and in their blood lipids after treatment at the Lipid Clinic?

(iv) How common is the presence of pancreatitis and CHD in this population?

3. Study design, study population and method

3.1 Study design

In the present study, already existing data was collected from medical records to the participants. The study was a retrospective and descriptive study.

3.2 Approvals

The study protocol was approved by the Regional Committee for Medical Research Ethics (appendix 1), in addition to the Data Inspectorate (appendix 2).

3.3 Study population

The study included individuals who were referred to the Lipid Clinic, Oslo University Hospital-Rikshospitalet, in the period 2002-2007. The patients were identified by searching the medical records for patients with the hypertriglyceridemia diagnoses (ICD-10 classification): pure hypertriglyceridemia (E78.1), mixed hyperlipidemia (E78.2) and hyperchylomicronemia (E78.3). To be included in the study the patients had to have a measured fasting TG level ≥10 mmol/L at some point during their treatment at the Lipid Clinic. The patients had to be 18 years or older.

In total, 112 patients from all over Norway fulfilled the inclusion criteria. These persons received a letter with information about the aim and form of the study, along with a consent form they were asked to sign and return if they agreed to participate in the study (appendix 3). Those who did not respond to the first information letter received the same letter once more. Finally, those who had not responded to neither of the letters were called and informed verbally about the study, and the importance of their participation. In total, 65 persons returned their written informed consent, and agreed to participate in the study (figure 4).

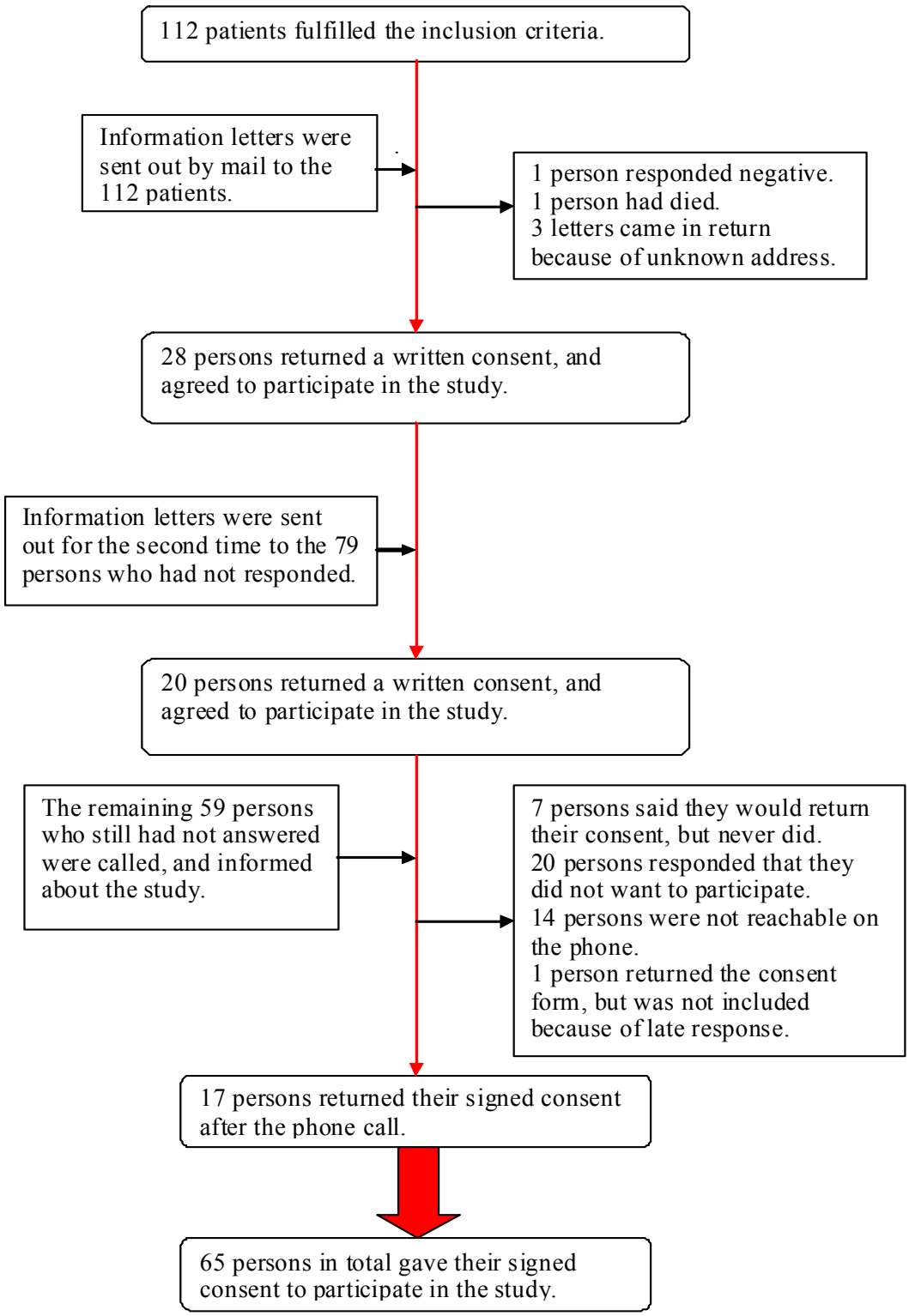

Figure 4. Flowchart showing the inclusion process of the participants.

3.4 Methods

3.4.1 Data collection

The medical records of the participants were used as a source for information in the present study. Data on age, diagnoses, clinical measures, blood samples, medications and lifestyle were collected from these records, and registered in an excel file. The data was de-identified by aid of identity numbers.

3.4.2 Visits to the Lipid Clinic

The included participants had their first visit to the Lipid Clinic at some point in the period 2002-2007. However, the number of visits, in addition to the period between each visit, was highly variable for the participants. Five of the patients had no registered follow-up at the Lipid Clinic after their consultation in this period. However, the median time of registered follow-up consultations was 2 years and 2 months.

3.4.3 Diagnoses

All the diagnoses which were recorded in the medical records were registered in the present study. Therefore, which diagnoses that were to be included were not determined at the start of the study, but rather during reading the medical records. Since several patients had more than one diagnosis, some of the patients have been recorded under several of the diagnoses. In the present study, the hyperlipidemias in the Fredrickson system were defined as primary diagnoses, while the other diagnoses were defined as secondary diagnoses.

All the diagnoses were made by a doctor, either before the patient came to the Lipid Clinic, or during the time there. One exception was the metabolic syndrome, which was diagnosed during this study in the patients that fulfilled the criteria for the diagnosis. Several definitions of the metabolic syndrome exist. Table 6 compares two of the customary definitions. The definition from the International Diabetes Federation requires an increased waist circumference in addition to at least two other

risk factors (127). In comparison, the definition from the National Cholesterol Education Program does not require an increased waist circumference, but states that all risk factors are equally important. According to this definition, ≥3 risk factors must be present in the patient (6). The definition from the National Cholesterol Education Program was used in the present study.

Table 6. Two commonly used definitions on the metabolic syndrome.

The National Cholesterol Education Program		**The International Diabetes Federation**	
≥3 of the following risk factors:	**Limit values:**	**Increased waist circumference + ≥2 other risk factors:**	**Limit values:**
Waist circumference (cm)		Waist circumference (cm)	
-men	>102	-men	≥94
-women	>88	-women	≥80
TG (mmol/L)	≥1.7	TG (mmol/L)	>1.7
HDL-cholesterol (mmol/L)		HDL-cholesterol (mmol/L)	
-men	<1.03	-men	<0.9
-women	<1.29	-women	<1.1
BP[1] (mmHg)	≥130/≥85	BP[1] (mmHg)	≥130/≥85
Fasting glucose[2] (mmol/L)	≥5.6	Fasting glucose[2] (mmol/L)	≥5.6

[1] The criteria is also fulfilled if the patient is treated medically for hypertension
[2] The criteria is also fulfilled if the patient has type 2 diabetes

Participants registered with pancreatitis in the present study included patients who had experienced pancreatitis before the start of treatment at the Lipid Clinic and/or during their time there. Similar, the category denoted CHD included both participants diagnosed with CHD before they came to the Lipid Clinic, in addition to participants who were diagnosed with CHD during their treatment there. CHD includes four different syndromes: (1) angina pectoris, (2) acute myocardial infarction, (3) sudden cardiac death, and (4) chronic ischemic heart disease with congestive heart failure (128).

Patients registered as having reumatic disease included participants with Bechterevs disease, arthritis, rheumatic arthritis and gout. The disease category denoted kidney disease, included patients with kidney failure and nephritis, while patients diagnosed with lung disease had either chronic obstructive pulmonary disease or asthma.

3.4.4 Medication

Information about type and doses of medications were collected from the medical records. Only lipid-lowering medications were registered, in addition to some other medications known to have an effect on the lipid profile, like anti-diabetic medications, xenical and antihypertensive medications.

3.4.5 The SmartDiet questionnaire

Lifestyle advice and recommendations for changes are an important part of the treatment at the Lipid Clinic. SmartDiet is a questionnaire with 25 questions about diet and lifestyle (appendix 4). All patients referred to the Lipid Clinic will fill out this questionnaire before each consultation. Based on the answers, the patients will receive recommendations with respect to lifestyle changes which can improve their lipid profile and health. The SmartDiet questionnaire is not available in the medical records to the patients, and information regarding the total score on this questionnaire was obtained from notes in the medical records made by the nutritionist or the doctor in the present study. Alterations in some of the measured lifestyle parameters were interpreted as possibly results of adherence to the recommendations they received at the Lipid Clinic.

It is possible to score 1 to 3 points on each question regarding the diet, where 1 equals a bad score and 3 a good score. The total sum of the scores is an estimation of the dietary habits to the individual (129). Based on these scores the doctor or nutritionist can give advice to the patients regarding how they can improve their diet.

The SmartDiet form was revised in 2007. The participants in the present study have therefore either used the oldest, newest, or both editions. However, both editions divide the total evaluation of the diet into three categories. The lowest score give the following characterisation of the diet: “You should improve your diet in several ways, to make it more heart-friendly”, a medium total score: “You can improve your diet, to make it more health- and heart friendly” and a high total score: “You have a healthy diet”. In this study each of these categories were denoted a score from 1 to 3

respectively. Change in total score from start to end of treatment was estimated and divided into following categories: the score was the same, worse or improved.

The category regarding alcohol intake have the following division in the SmartDiet questionnaire: no, little (<1 unit per week), moderate (1-7 units per week), high (8-14 units per week) and very high (>15 units per week). One unit is defined as 125 ml wine or 0.33 l beer or 4 cl spirits. Each category was in the present study given a score from 0 to 4 respectively. To investigate the mean alcohol intake, all the reported scores on alcohol intake were added and then divided on the total number of scores registered for each patient. Regarding smoking habits, the different categories are: no, party smoker and smoking at a daily basis. Degree of physical activity is divided into: 0-1 time per week, 1-2 times per week and ≥3 times per week. One time is defined as physical performance for at least 30 minutes, for instance swimming, running, skiing or bicycling.

Not all the participants had answered the SmartDiet questionnaire. The information regarding diet and lifestyle was therefore incomplete for many of the patients.

3.4.6 Clinical measurements

Height, weight, waist circumference and blood pressure (BP) were identified in the medical records. By aid of this information, it was possible to estimate the Body mass index (BMI) for each participant. BMI is an index of weight-for-height that is commonly used to classify underweight, overweight and obesity in adults. BMI is defined as weight in kilograms divided by the square of the height in metres (kg/m^2). WHO defines BMI <18.5 kg/m^2 as underweight, BMI 18.5-24.9 kg/m^2 as normal weight, BMI 25.0-29.9 kg/m^2 as overweight and BMI >30 kg/m^2 as obesity (130). Some of the participants had never taken these measurements, while others had taken them several times. As a consequence, the information about many of these parameters was incomplete.

Time intervals were defined to decide which measurements were to be included, and to make it possible to estimate the change in these parameters following baseline

(table 7). The baseline values refer to the measurements taken at the first visit to the Lipid Clinic. To ensure that as much data as possible would be included in the analyses, results from measurements taken after 0.5, 1, 2 and 3 years following baseline were selected. However, since the time between the measures was highly variable, clinical measurements taken 3 months before/after these specified times were also included. For those participants with only one registered measure, it was not possible to calculate the change after a treatment period. After plotting all the clinical measurements for each patient on each time interval, it became clear that only a small number of participants had a registered waist circumference following baseline. Therefore, the alterations following baseline were only estimated for weight and blood pressure.

Table 7. Time intervals for included clinical findings and blood parameters.

	Time intervals
Baseline	At the start of treatment
0.5 years	6 months ± 3 months after baseline
1 year	1 year ± 3 months after baseline
2 years	2 years ± 3 months after baseline
3 years	3 years ± 3 months after baseline

3.4.7 Blood samples

Nineteen different blood parameters of interest were collected from the medical records of the patients and used in the study. The parameters were the following: glucose, HbA1c, serum-insulin, c-peptide, total-cholesterol, LDL-cholesterol, HDL-cholesterol, TG, lipoprotein little a (Lp (a)), apo A1, apo B, c-reactive protein (CRP), thyroidea-stimulating hormone (TSH), free thyroxin (FT_4), aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), creatinine kinase (CK), creatinine and pancreas amylase. These blood parameters were taken after at least 12 hours fasting, and were analyzed at Oslo University Hospital-Rikshospitalet. Laboratory results which were reported as Lp (a) values <100 mg/L and CRP values <10 mg/L were not included since these results were to unspecified.

Not all the participants had measured these 19 blood parameters. In addition, some of them had only taken one blood sample, while others had taken several. The time intervals which decided which blood samples were to be included in the study were the same as for the clinical measurements (table 7). In addition to values measured in these time intervals, the referral values for TG levels were also included in some analyses. These values represent those who were reported in the referral letters, which were sent to the Lipid Clinic by the general practitioners of the patients. Results from the blood samples were registered in an excel file with a column for each parameter measured at different times, and a row for each individual.

3.4.8 Triglyceride quartiles

Since the TG values taken at the first visit at the Lipid Clinic showed a wide distribution, the participants were divided into quartiles according to their first measured TG values, so these four groups could be compared with respect to clinical findings and secondary diagnoses, and to make it possible to determine if those with the highest TG values at the start of treatment differed from the rest of the patients. The patients were divided into the following groups: (1) patients with TG ≤10 mmol/L, (2) patients with TG >10 mmol/L and ≤20 mmol/L, (3) patients with TG >20 mmol/L and ≤30 mmol/L, and (4) patients with TG >30 mmol/L.

3.4.9 Statistics

All statistical analyses were performed with SPSS (Statistical Package for the Social Sciences) version 16.0. First the data were checked to decide whether they fulfilled the criteria for a normal distribution. This was done by the Shapiro- Wilks normality test, and evaluation of histograms and Q-Q-plots. Most of the data did not show a normal distribution, and non-parametric statistical analyses were therefore mainly used. Results from non-parametric statistical analyses are reported as median and 95 % confidence interval (95 % CI) to the median. Results from variables that showed a normal distribution are reported as mean and standard deviation (SD) of the mean. P-values less than 0.05 were considered as statistically significant. Wilcoxon Signed Rank Test and Paired-Samples T-Test were used to evaluate the change in clinical

measures and blood parameters. Chi-square test for independence and Mann-Whitney U Test were used to detect possible differences in patients with and without CHD and pancreatitis. McNemar`s test was used to evaluate possible alterations in the use of medications and in lifestyle parameters following baseline. Kruskal-Wallis Test was used to compare clinical findings in patients divided into groups according to their TG values (TG quartiles). Logistic regression was used to determine how well different variables could explain the presence of CHD in the present study.

4. Results

Sixty-five out of the 112 patients (58 %) that fulfilled the inclusion criteria agreed to participate in the present study. Among the participants, 51 were men and 14 were women. The mean age was 45.8 years.

4.1 Diagnoses

All the participants had either a primary diagnosis, one or several secondary diagnoses or combinations of both primary and secondary diagnoses registered in their medical records, except for one patient.

4.1.1 Primary hypertriglyceridemia

Among the participants, only 28 patients had a registered primary diagnosis that could explain their hyperlipidemia. These diagnoses were based on genetic findings and/or clinical and familial characteristics typical for primary hyperlipidemias (table 8). Familial combined hyperlipidemia was the primary diagnosis with highest occurrence in the present study, and was diagnosed in 17 patients (26 %). Gene tests and available information about familial disposition could, however, not explain the hyperlipidemia in the rest of the patients. Among those without a confirmed primary cause of their hypertriglyceridemia, 19 participants were referred to the Lipid Clinic based on combined hyperlipidemia, and 18 participants for hypertriglyceridemia. However, 2 of these patients possibly had a primary mixed hyperlipidemia (type V), but this diagnosis was not completely confirmed.

All of those with a primary cause of their hyperlipidemia had one or several secondary diagnoses in addition, with the exception of one person diagnosed with primary mixed hyperlipidemia. There were no significant differences in the presence of various secondary diagnoses between the groups of primary diagnoses. Table 9 contains information about the occurrence of the most common secondary conditions seen in patients with a primary diagnosis.

Table 8. Number of patients with primary hyperlipidemias.

Dyslipidemia	Fredricksons classification	ICD-10	n
Familial chylomicronemia	Type I	E78.3	0
Familial hypercholesterolemia	Type IIa	E78.0	0
Familial combined hyperlipidemia	Type IIb	E78.4	17
Familial dysbetalipoproteinemia	Type III	E78.2	3
Familial hypertriglyceridemia	Type IV	E78.1	2
Primary mixed hyperlipidemia	Type V	E78.3	6
Total			28

Table 9. Secondary diagnoses in combination with primary hyperlipidemias.

Fredricksons classification	Type IIb n=17		Type III n=3		Type IV n=2		Type V n=6	
Secondary diagnoses	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**
Metabolic syndrome	83	15	67	2	100	2	83	5
Hypertension	50	9	33	1	0	0	50	3
CHD	39	7	33	1	0	0	33	2
Type 2 diabetes	22	4	33	1	50	1	50	3
Reumatic disease	39	7	33	1	0	0	17	1
Pancreatitis	17	3	0	0	0	0	50	3
Hypothyroidism	11	2	33	1	50	1	17	1

4.1.2 Secondary hypertriglyceridemia

Thirty-seven participants had no primary diagnosis recorded in their medical records. However, nearly all had one or several secondary conditions in addition to their hyperlipidemia. Thus, their hyperlipidemia might therefore be a result of the presence of these conditions (secondary hyperlipidemia). Considering the whole study population, over 60 % had ≥3 secondary diagnoses recorded in their medical records (table 10). One of the patients without a secondary diagnosis had a registered primary cause that could explain the hyperlipidemia, namely a primary mixed hyperlipoproteinemia. Only one patient had no registered primary or secondary conditions. The metabolic syndrome, hypertension and type 2 diabetes were the diagnoses most frequently seen in this group of patients (figure 5).

Table 10. Number of patients with no /several secondary diagnoses.

Number of secondary diagnoses	Number of patients	
	n	%
0	2	3.1
1	11	16.9
2	11	16.9
≥3	41	63.1
Total	65	100

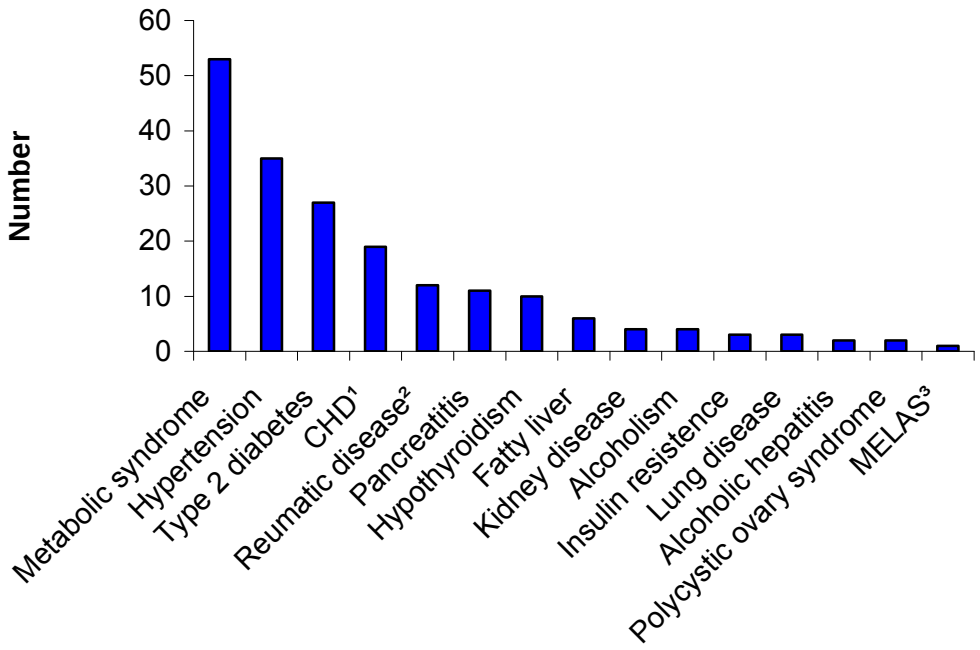

Figure 5. Number of patients with different secondary diagnoses, n=65.

[1] Includes patients with established CHD before they came to the Lipid Clinic and patients who were diagnosed with CHD during the time they were patients at the Lipid Clinic.
[2] Four of the 12 patients with reumatic disease had arthritis urica.
[3] MELAS, Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes.

4.2 Treatment of hypertriglyceridemia

All the participants used one or several medications in their treatment at the Lipid Clinic, except for 4 patients. However, they all received advice and recommendations regarding a healthy lifestyle and diet, either in group or at individual consultations with a nutritionist.

4.2.1 Medications

Half of the study population (n=33) used one or several lipid-lowering medications when they first came to the Lipid Clinic. However, this group of patients did not include all of those with the highest reported TG concentration in the referral letters. For instance, no medication therapy was initiated for a patient with reported TG concentration of 62.5 mmol/L. Among those who already used medications, statins were the most commonly used medication group, where atorvastatin was the type most utilized. As many as 28 patients reported intake of different fish oil preparations, where 11 of these used the concentrated omega-3 preparation, Omacor, in different doses. Several patients also used medications in combination. Statins were included in all these combinations, and were used together with either Omacor (n=6), resins (n=1) or Omacor in addition to a fibrate (n=1).

At the last consultation, 89 % of the participants used one or several lipid-lowering medications. This represents a significant increase in the number of patients who started on lipid-lowering medications after they came to the Lipid Clinic ($p < 0.001$). There was an increase in the use of statins, as well as fibrates. However, the greatest change was in the use of Omacor. Thirty-one more patients used this medication at their last consultation compared to baseline. In addition, the majority used several medications in combination (table 11). Only 7 patients used statins alone, 2 patients used fibrates alone and 6 patients used Omacor alone. The remainder used up to four preparations simultaneously. Table 12 contains information about type and doses of lipid-lowering medications which were used at the start and end of treatment at the Lipid Clinic.

In total, 53 participants used statins at some point during their treatment at the Lipid Clinic, 46 participants used Omacor, 30 participants used fibrates, and 11 participants used other lipid-lowering medications (ezetimibe, nicotinic acid, resins). Four patients did not use any lipid-lowering medications at all.

Some patients used other medications in addition to the lipid-lowering types, for instance Xenical (n=5), thyroxine (n=9) and antidiabetica (n=20). Regarding

medications which might contribute to elevated TG levels, 24 patients used antihypertensive medications when they came to the Lipid Clinic, and 35 patients in total used antihypertensive medications during their treatment at the Lipid Clinic. In addition, one patient used resins at the start of treatment at the Lipid Clinic, while 5 patients in total used resins at some point during their treatment at the Lipid Clinic. All the patients who used resins in their treatment used other lipid-lowering medications in addition.

Table 11. Combinations of medications used at the end of treatment, n=43.

Combinations	n
Statin + Omacor	16
Statin + Fibrate	4
Fibrate + Omacor	3
Statin + Ezetimibe	1
Statin + Omacor + Fibrate	11
Statin + Omacor + Ezetimibe	2
Omacor + Ezetimibe + Resin	1
Statin + Fibrate + Ezetimibe	1
Statin + Ezetimibe + Nicotinic acid	1
Nicotinic acid + Omacor + Ezetimibe	1
Statin + Omacor + Fibrate + Ezetimibe	2

Table 12. Medications used at the Lipid Clinic, n=65.

Type and dose		At the start of treatment, n=33		At the end of treatment, n=58	
		%	n	%	n
Statins:		**44.6**	**29**	**69.2**	**45**
Atorvastatin:	10 mg	0	0	4.4	2
	20 mg	0	0	13.3	6
	40 mg	24.1	7	24.4	11
	60 mg	6.9	2	0	0
	80 mg	20.7	6	20.0	9
Simvastatin:	20 mg	6.9	2	6.7	3
	40 mg	6.9	2	22.2	10
	80 mg	10.3	3	0	0
	120 mg	3.5	1	0	0
Fluvastatin:	20 mg	0	0	2.2	1
	40 mg	3.5	1	0	0
Pravastatin:	20 mg	3.5	1	0	0
	40 mg	6.9	2	4.4	2
	80 mg	3.5	1	0	0
Unknown		3.5	1	2.2	1
Fibrates:		**1.5**	**1**	**35.4**	**23**
Bezafibrate:	200 mg	0	0	4.3	1
	400 mg	0	0	13.0	3
	4200 mg	0	0	4.3	1
Fenofibrate:	160 mg	0	0	4.3	1
	200 mg	0	0	69.6	16
	300 mg	100.0	1	4.3	1
Fish-oil/Omacor:		**16.9**	**11**	**64.6**	**42**
Omacor:	840 mg x2	9.1	1	9.5	4
	840 mg x3	0	0	2.4	1
	840 mg x4	9.1	1	14.3	6
	840 mg x5	0	0	4.8	2
	840 mg x6	81.8	9	64.3	27
	840 mg x8	0	0	2.4	1
	Unknown	0	0	2.4	1
Ezetimibe:		**0**	**0**	**13.8**	**9**
Ezetrol:	10 mg	0	0	100.0	9
Nicotinic acid:		**0**	**0**	**3.1**	**2**
Niaspan:	2000 mg	0	0	100.0	2
Resins:		**1.5**	**1**	**1.5**	**1**
	1200 mg	100.0	1	0	0
	3750 mg	0	0	100.0	1

4.2.2 Lifestyle changes

As one can see in figure 6, 31 patients reported at their first consultation that they never smoked, and just as many said they smoked daily. Regarding degree of physical activity, 28 patients answered that they were seldom active. This equals 43 % of the study population. The majority consumed alcohol, but to a varying degree. However, alcohol intake in moderate amounts (1-7 units per week) was most frequently reported. The reported lifestyle parameters did not change significantly from the first and to the last time the patients were asked how often they smoke, drink alcohol and perform physical activity.

Regarding the 4 participants who did not use any lipid-lowering medications in their treatment, their lifestyle changes were not striking either. Only 2 of them made some positive changes with respect to their diet, and one of these patients also reduced the intake of alcohol.

Results from the SmartDiet questionnaire (table 13) showed that the majority of the patients had a medium score both the first time and the last time they answered the questionnaire. The change in total score was not significant (p=0.06). However, approximately 37 % obtained a better total score, 50 % the same score and 13 % a worse score when considering the change in reported diet.

Table 13. Results from the SmartDiet questionnaire.

	SCORE 1		2		3		Total	
	%	n	%	n	%	n	%	n
First time [1]	16.1	10	72.6	45	11.3	7	100	62
Last time [2]	15.8	6	52.6	20	31.6	12	100	38
Change [3]	13.2	5	50.0	19	36.8	14	100	38

[1] Total score the first time the patients answered the SmartDiet questionnaire.
[2] Total score the last time the patients answered the SmartDiet questionnaire.
[3] Change in total score when comparing results from the first and last time the patients answered the questionnaire. Score 1, a worse score; score 2, the same score; score 3, a better score.

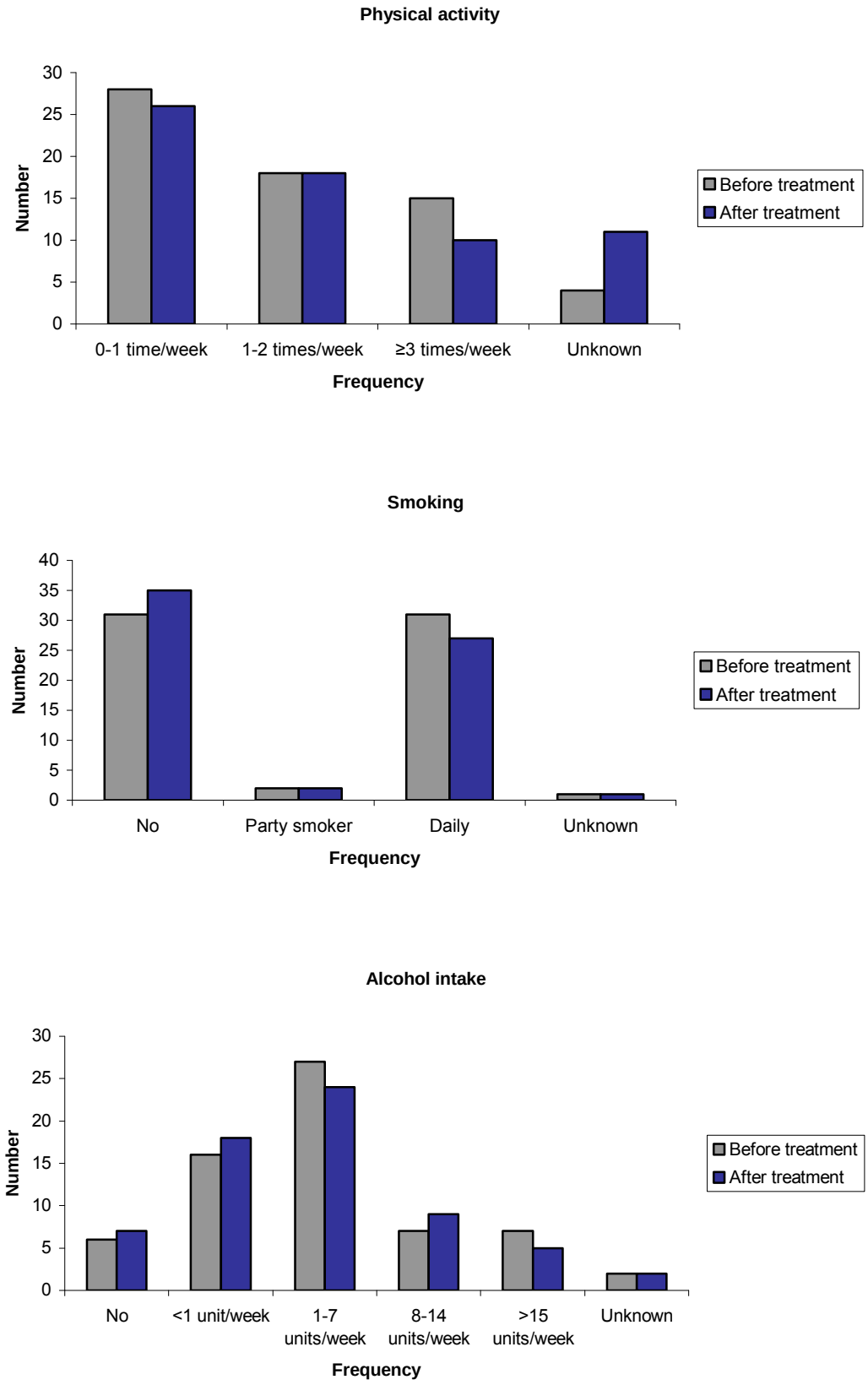

Figure 6. Frequency of physical activity, smoking and alcohol intake, n=65.

4.3 Baseline characteristics and effects of the treatment

4.3.1 Clinical measurements

The mean BMI was 29.2 kg/m^2 when the participants first came to the Lipid Clinic for consultation. Only 14.5 % of the patients had a BMI in the normal range, 50 % were overweight and 35.5 % were obese. The waist circumference ranged between 91–128 cm for the women (n=8), and 95–116 cm for the men (n=19). More descriptive information is found in table 14.

The body weight to the participants did not change significantly following baseline (table 15). However, the median blood pressure showed a reduction (table 16). The values were significantly lower after 1 and 2 years compared to the baseline values, both for systolic and for diastolic blood pressure.

Table 14. Descriptive information of the patients at their first consultation, n=65.

Demographics	**n**		
Men/ women	51/ 14		
Age (years) [a]	65	45.8	(28–73)
Weight (kg) [b]	62	90.8	(15.2)
Height (cm) [b]	64	176.0	(8.4)
BMI (kg/m^2) [b]	62	29.2	(4.1)
Waist (cm) [b]	27	104.9	(7.4)
Systolic BP (mmHg) [c]	57	142.0	(136.0–147.0)
Diastolic BP (mmHg) [c]	57	88.0	(86.0–95.0)

[a] mean, (minimum–maximum)
[b] mean and standard deviation (SD)
[c] Median, 95 % confidence interval (CI)

Table 15. Body weight measures following baseline, mean and SD.

Time	**Weight (kg)**	**P-values**
Baseline, n=62	90.8 ± 15.2	
0.5 years, n=20	89.7 ± 15.7	0.885 [1]
1 year, n=29	90.7 ± 15.6	0.851 [2]
2 years, n=16	95.0 ± 13.1	0.404 [3]
3 years, n=11	86.3 ± 14.5	0.479 [4]

[1] Comparison of weight after 0.5 years with weight at baseline, n=19
[2] Comparison of weight after 1 year with weight at baseline, n=28
[3] Comparison of weight after 2 years with weight at baseline, n=15
[4] Comparison of weight after 3 years with weight at baseline, n=10

Table 16. Blood pressure measurements following baseline, median and 95 % CI.

	Systolic BP (mmHg)	P-values [a]	Diastolic BP (mmHg)	P-values [b]
Baseline, n=57	142.0 (136.0–147.0)		88.0 (86.0–95.0)	
0.5 years, n=14	130.5 (121.0–135.0)	0.084 [1]	83.0 (65.0–93.0)	0.314 [1]
1 year, n=23	135.0 (126.0–137.0)	**0.012** [2]	86.0 (84.0–92.0)	**0.031** [2]
2 years, n=17	130.0 (125.0–138.0)	**0.002** [3]	85.0 (82.0–90.0)	**0.035** [3]
3 years, n=10	119.5 (110.0–151.0)	0.126 [4]	80.5 (78.0–89.0)	0.128 [4]

[a] P-values for systolic BP
[b] P-values for diastolic BP
[1] Comparison of BP after 0.5 years with BP at baseline, n=13
[2] Comparison of BP after 1 year with BP at baseline, n=21
[3] Comparison of BP after 2 year with BP at baseline, n=15
[4] Comparison of BP after 3 years with BP at baseline, n=7

4.3.2 Blood sample measures

Table 17 contains information about TG values reported in the referral letters to the patients and values measured at baseline at the Lipid Clinic. The TG values measured at baseline were not significantly altered compared to the values reported in their referral letters. However, when only considering participants with TG values ≥10 mmol/L in the referral letters, there was a significant reduction at baseline.

Table 17. TG values at referral compared to baseline values.

	n	Median	95 % CI	Minimum	Maximum	P-values
TG at referral, mmol/L	54	12.7	(10.4–16.5)	3.3	65.0	0.356 [1]
TG ≥10 mmol/L at referral	37	16.9	(13.1–19.3)	10.3	65.0	**0.012** [2]
TG at baseline, mmol/L	64	12.3	(10.2–15.5)	2.8	57.3	

[1] Comparison of TG values measured at baseline with TG values reported in referral letters, n=53.
[2] Comparison of TG values measured at baseline with TG values reported in referral letters to patients who had TG ≥10 mmol/L at referral, n=36.

According to the recommended values for blood lipids from the Norwegian Medicines Agency (78), only the median total-cholesterol and TG values were elevated in the participants at their first consultation at the Lipid Clinic. The median concentrations of other blood parameters were within the reference values stated by the Clinical chemical division, Oslo University Hospital-Rikshospitalet (131) (table 18). The minimum TG value was 2.8, and the maximum value was 57.3 mmol/L. This represents a huge variation among the participants with respect to TG values at baseline. The female participants had significantly higher TG values, measured at

their first visit, compared to the males (p=0.011). The median TG value was 18.4 mmol/L (95 % CI: 10.2–28.8) and 11.4 mmol/L (95 % CI: 8.8–14.1) for the women and men respectively.

Table 18. Blood parameters measured at the start of treatment at the Lipid Clinic.

Blood parameters	n	Median	95 % CI	Reference
Glucose, mmol/L	51	5.8	(5.6–6.1)	4.0-6.0 [a]
HbA1c, %	44	5.6	(5.4–5.8)	4.5-6.5 [a]
Insulin, ρmol/L	26	82.5	(48.0–97.0)	21.0-210.0 [a]
C-peptide, nmol/L	35	1.2	(1.0–1.4)	0.3-2.4 [a]
Total-cholesterol, mmol/L	62	**8.0**	(6.9–9.6)	<5.0 [b]
LDL-cholesterol, mmol/L	35	2.3	(1.9–3.3)	<3.0 [b]
HDL-cholesterol, mmol/L	58	1.1	(1.0–1.2)	>1.0 [b]
TG, mmol/L	64	**12.3**	(10.2–15.5)	<2.0 [b]
Apo A1, g/L	35	1.2	(1.1–1.3)	M:1.1-1.8 / W:1.2-2.3 [a]
Apo B, g/L	40	1.0	(0.9–1.1)	0.5-1.3 [a]
Lp (a), mg/L	18	114.0	(87.0–315.0)	[c]
TSH, mIE/L	43	1.8	(1.3–2.2)	M:0.5-3.6 / W:0.5-3.4 [a]
FT_4, ρmol/L	43	13.9	(13.0–14.8)	9.0-21.0 [a]
CRP, mg/L	42	2.2	(1.7–2.8)	<4.0 [a]
ASAT, U/L	47	35.0	(30.0–40.0)	M:15.0-45.0 / W:15.0-35.0 [a]
ALAT, U/L	52	44.0	(35.0–56.0)	M:10.0-70.0 / W:10.0-45.0 [a]
CK, U/L	37	116.0	(97.0–158.0)	M:<270.0 / W:<150.0 [a]
Kreatinin, µmol/L	43	76.0	(70.0–86.0)	M:60.0-105.0 / W:50.0-90.0 [a]
Pancreas amylase, U/L	27	24.0	(19.0–29.0)	10.0-65.0 [a]

[a] Clinical chemical division, Oslo University Hospital-Rikshospitalet.
[b] The Norwegian Medicines Agency, therapy recommendations 2003.
[c] Clinical chemical division, Oslo University Hospital-Rikshospitalet: 75 % of the population has Lp (a) <300 mg/L
M, men; W: women

The TG values measured after 0.5, 1 and 3 years following baseline were significantly lower compared to the baseline values (figure 7). In addition, the total-cholesterol values showed a significantly reduction at all times compared to baseline (figure 8). However, despite this reduction, the concentration of both TG and total-cholesterol were still above the recommended 3 years following baseline. The LDL-cholesterol and apo A1 values did not change significantly following baseline (figure 9 and figure 11). However, the HDL-cholesterol and apo B values were significantly reduced after one year of treatment (figure 10 and figure 12). More information can be found in table 19.

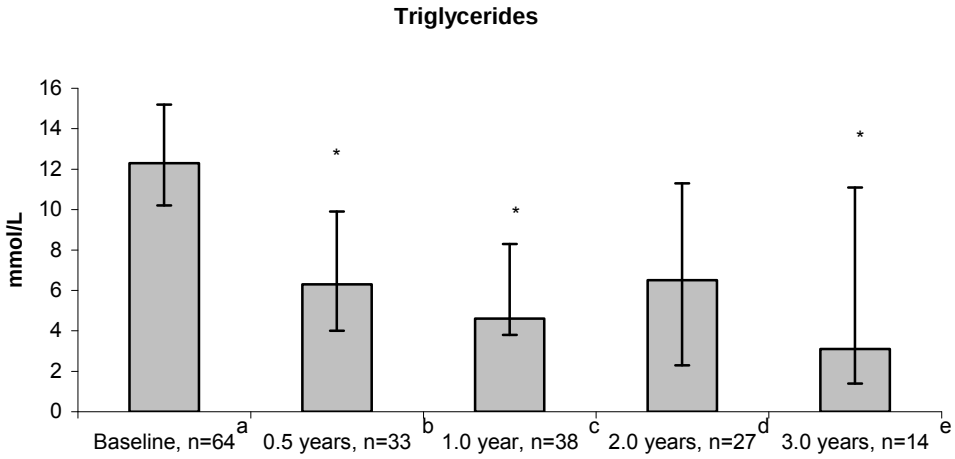

Figure 7. TG values at baseline and following baseline, median (95 % CI).

* Significant lower values compared to baseline values.
[a] Baseline, measurements taken at the first consultation at the Lipid Clinic
[b] 0.5 years, measurements taken 6 months (±3 months) after baseline.
[c] 1.0 year, measurements taken 1 year (±3 months) after baseline.
[d] 2.0 years, measurements taken 2 years (±3 months) after baseline.
[e] 3.0 years, measurements taken 3 years (±3 months) after baseline.

Figure 8. Total-cholesterol at baseline and following baseline, median (95 % CI).

* Significant lower values compared to baseline values.
[a] Baseline, measurements taken at the first consultation at the Lipid Clinic
[b] 0.5 years, measurements taken 6 months (±3 months) after baseline.
[c] 1.0 year, measurements taken 1 year (±3 months) after baseline.
[d] 2.0 years, measurements taken 2 years (±3 months) after baseline.
[e] 3.0 years, measurements taken 3 years (±3 months) after baseline.

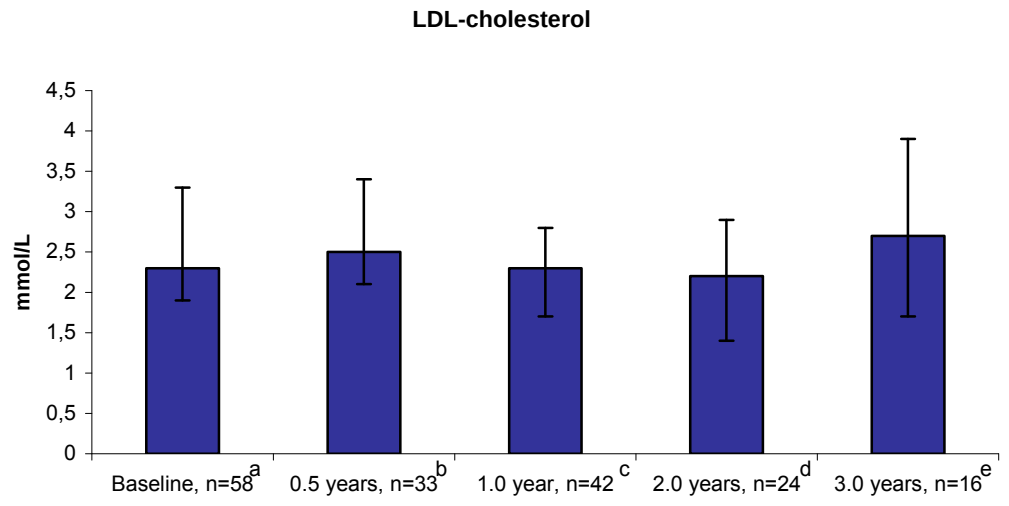

Figure 9. LDL-cholesterol at baseline and following baseline, median (95 % CI).

[a] Baseline, measurements taken at the first consultation at the Lipid Clinic
[b] 0.5 years, measurements taken 6 months (±3 months) after baseline.
[c] 1.0 year, measurements taken 1 year (±3 months) after baseline.
[d] 2.0 years, measurements taken 2 years (±3 months) after baseline.
[e] 3.0 years, measurements taken 3 years (±3 months) after baseline.

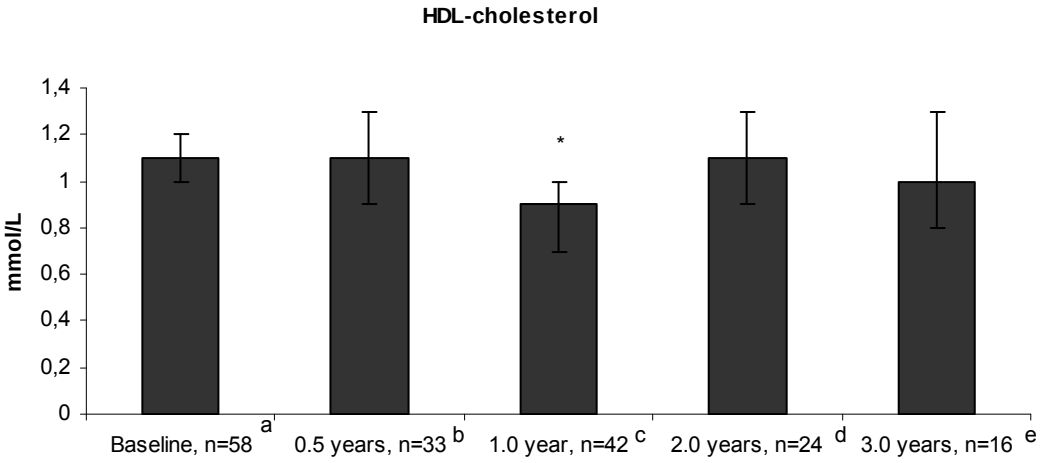

Figure 10. HDL-cholesterol at baseline and following baseline, median (95 % CI).

* Significant lower values compared to baseline values.
[a] Baseline, measurements taken at the first consultation at the Lipid Clinic
[b] 0.5 years, measurements taken 6 months (±3 months) after baseline.
[c] 1.0 year, measurements taken 1 year (±3 months) after baseline.
[d] 2.0 years, measurements taken 2 years (±3 months) after baseline.
[e] 3.0 years, measurements taken 3 years (±3 months) after baseline.

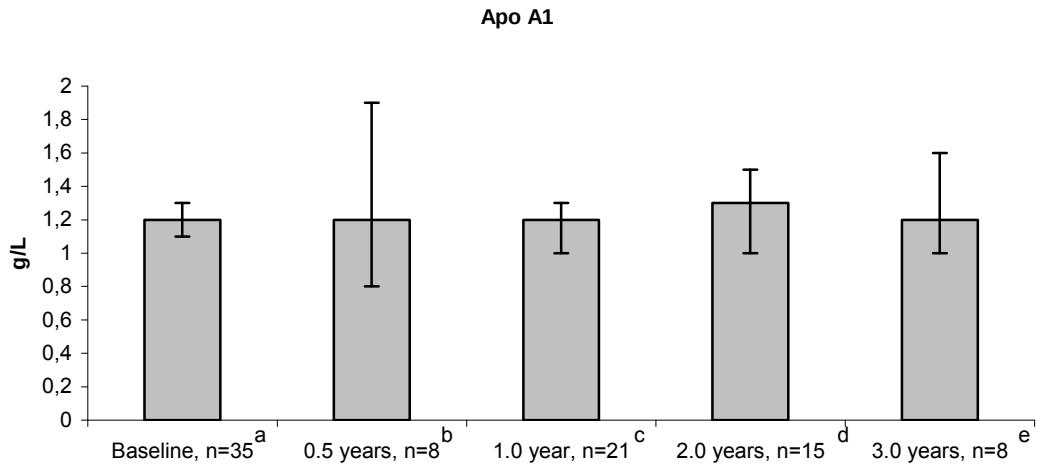

Figure 11. Apo A1 values at baseline and following baseline, median (95 % CI).

[a] Baseline, measurements taken at the first consultation at the Lipid Clinic
[b] 0.5 years, measurements taken 6 months (±3 months) after baseline.
[c] 1.0 year, measurements taken 1 year (±3 months) after baseline.
[d] 2.0 years, measurements taken 2 years (±3 months) after baseline.
[e] 3.0 years, measurements taken 3 years (±3 months) after baseline.

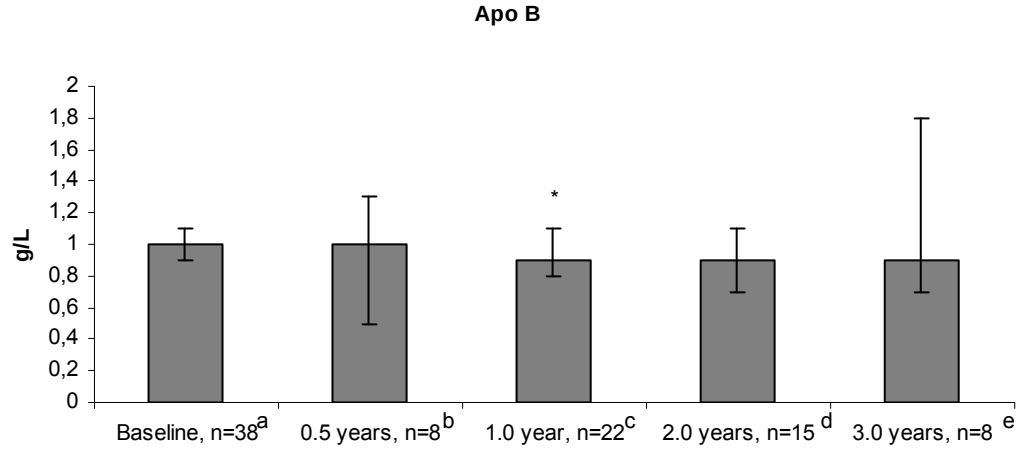

Figure 12. Apo B values at baseline and following baseline, median (95 % CI).

* Significant lower values compared to baseline values.
[a] Baseline, measurements taken at the first consultation at the Lipid Clinic
[b] 0.5 years, measurements taken 6 months (±3 months) after baseline.
[c] 1.0 year, measurements taken 1 year (±3 months) after baseline.
[d] 2.0 years, measurements taken 2 years (±3 months) after baseline.
[e] 3.0 years, measurements taken 3 years (±3 months) after baseline.

Table19. Blood parameters measured at different times following baseline, median (95 % CI).

	Baseline	After 0.5 years	After 1 year	After 2 years	After 3 years	P1	P2	P3	P4
Total-cholesterol, mmol/L	8.0 (6.9–9.6)	6.2 (5.0–7.8)	5.5 (4.7–6.3)	5.5 (4.8–6.4)	5.8 (4.7–8.6)	**0.032**	**<0.001**	**0.032**	**0.015**
n	62	34	42	28	14	32	40	27	13
LDL-cholesterol, mmol/L	2.3 (1.9–3.3)	2.5 (2.1–3.4)	2.3 (1.7–2.8)	2.2 (1.4–2.9)	2.7 (1.7–3.9)	0.432	0.911	0.837	0.262
n	35	23	35	21	14	15	20	11	8
HDL-cholesterol, mmol/L	1.1 (1.0–1.2)	1.1 (0.9–1.3)	1.0 (0.9–1.1)	1.1 (0.9–1.3)	1.0 (0.8–1.3)	0.299	**0.006**	0.522	0.059
n	58	33	42	24	16	31	37	21	15
TG mmol/L	12.3 (10.2–15.5)	6.3 (4.0–9.9)	4.6 (3.8–8.3)	6.5 (2.3–11.3)	3.1 (1.4–11.1)	**0.015**	**<0.001**	0.166	**0.006**
n	64	33	38	27	15	32	38	27	15
Apo A1 g/L	1.2 (1.1–1.3)	1.2 (0.8–1.9)	1.2 (1.0–1.3)	1.3 (1.0–1.5)	1.2 (1.0–1.6)	0.914	0.418	0.498	0.564
n	35	8	21	15	8	7	14	7	3
Apo B g/L	1.0 (0.9–1.1)	1.0 (0.5–1.3)	0.9 (0.8–1.1)	0.9 (0.7–1.1)	0.9 (0.7–1.8)	0.595	**0.035**	0.131	0.414
n	38	8	22	15	8	7	14	7	3
Glucose mmol/L	5.8 (5.6–6.1)	6.1 (5.2–6.6)	6.1 (5.7–6.5)	6.7 (5.6–8.7)	6.3 (5.0–13.3)	0.887	0.466	**0.004**	0.446
n	51	18	30	19	10	17	27	18	8

P1, Comparison of baseline values and values taken after 6 months (±3 months).
P2, Comparison of baseline values and values taken after 1 year (±3 months).
P3, Comparison of baseline values and values taken after 2 years (±3 months).
P4, Comparison of baseline values and values taken after 3 years (±3 months).

The TG values to the patients who did not use medications during their treatment at the Lipid Clinic are listed in table 20. They all had high or very high TG levels at the start of treatment. After consultations at the Lipid Clinic, their TG levels showed a reduction, although it was not significant (p=0.068).

Table 20. TG levels to patients who were not treated medically, n=4.

First TG values[1] (mmol/L)	Last TG values[2] (mmol/L)	Minimum TG values (mmol/L)	Maximum TG values (mmol/L)	Reduction in TG values (%)
17.9	16.0	16.0	17.9	10.6
4.9	4.0	1.9	11.2	18.4
9.8	3.7	3.7	10.9	62.3
12.4	3.9	3.9	12.4	68.5

[1] The first measured TG values at the Lipid Clinic.
[2] The last measured TG values at the Lipid Clinic taken after minimum 1 month and maximum 3.3 years.

4.3.3 Triglyceride quartiles

The patients were divided into quartiles according to their first measured TG values, and table 21 contains information about clinical findings in the different groups. There were no significantly differences between the groups with respect to age, weight, BMI, waist or diastolic blood pressure. Only the systolic blood pressure was significantly higher in the patients with TG between 10 mmol/L and 20 mmol/L, compared with those who had TG ≤10 mmol/L (p=0.008).

The presence of ≥3 diagnoses in addition to their hyperlipidemia was common in all the groups (figure 13). Figure 14 shows the occurrence of those diagnoses which varied most between the groups. The conditions not included varied only in a small degree, and are therefore not presented in this figure. Hypertension, type 2 diabetes and CHD were the most common secondary diagnoses in patients with TG values between 20 mmol/L and 30 mmol/L, while alcoholism and pancreatitis were mostly seen in patients who had TG values >30 mmol/L.

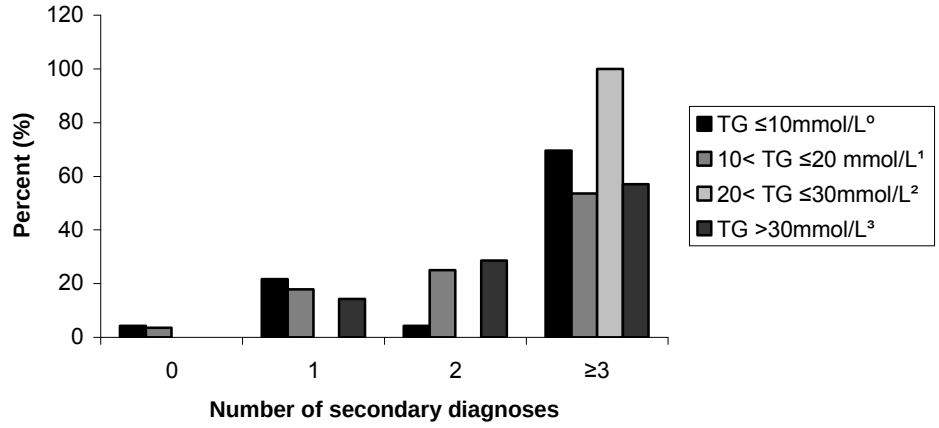

Figure 13. Number of secondary diagnoses in patients divided into quartiles, n=64.

° Patients with TG ≤10 mmol/L at their first consultation, n=23
¹ Patients with 10< TG ≤20 mmol/L at their first consultation, n=28
² Patients with 20< TG ≤30 mmol/L at their first consultation, n=6
³ Patients with TG >30 mmol/L at their first consultation, n=7

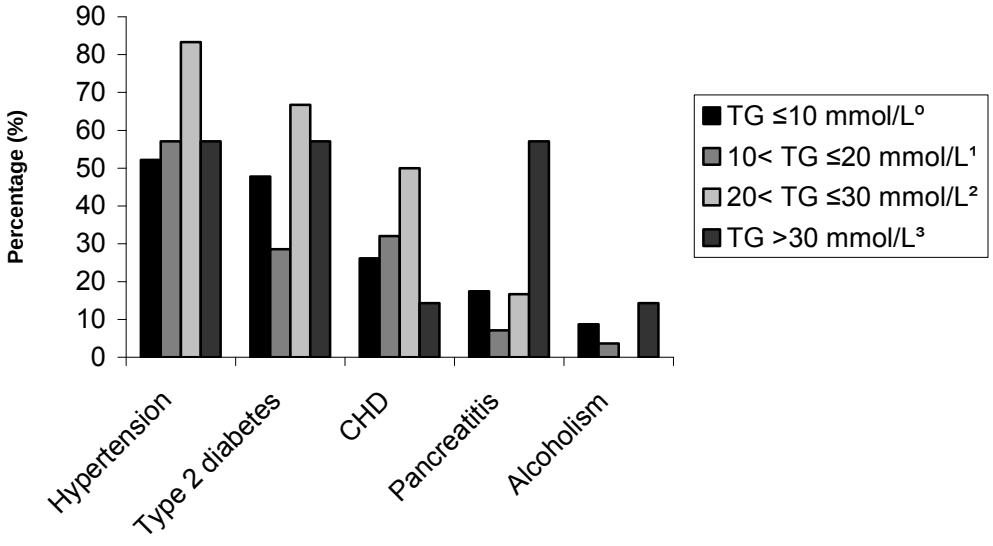

Figure 14. Specific secondary diagnoses in patients divided into quartiles, n=64.

° Patients with TG ≤10 mmol/L at their first consultation, n=23
¹ Patients with 10< TG ≤20 mmol/L at their first consultation, n=28
² Patients with 20< TG ≤30 mmol/L at their first consultation, n=6
³ Patients with TG >30 mmol/L at their first consultation, n=7

Table 21. Characteristics of the patients in each group, median (95 % CI), n=64.

TG, mmol/L	≤10	n	>10 – ≤20	n	>20 – ≤30	n	>30	n
TG, mmol/L	6.1 (4.9–6.9)	23	14.2 (12.2–16.2)	28	25.9 (21.1–28.8)	6	43.4 (36.8–57.3)	7
Age, [a] years	43.0 (28.0–63.0)	23	47.5 (28.0–73.0)	28	48.5 (37.0–57.0)	6	37.0 (31.0–52.0)	7
Weight, kg	89.0 (83.0–96.0)	22	89.4 (84.0–96.0)	26	83.6 (79.1–117.0)	6	96.0 (60.5–117.0)	7
BMI, kg/m^2	28.0 (26.3–31.0)	22	28.6 (27.7–29.9)	26	30.9 (26.4–38.6)	6	33.4 (24.0–36.9)	7
Waist, cm	104.0 (96.0–110.0)	11	105.5 (100.0–114.0)	10	103.0 (101.0–103.0)	3	107.0 (91.0–108.0)	3
Systolic BP, mmHg	130.0 (120.0–145.0)	19	149.0 (139.0–154.0)	24	137.0 (120.0–168.0)	5	144.0 (121.0–160.0)	6
Diastolic BP, mmHg	88.0 (80.0–96.0)	19	94.0 (86.0–98.0)	24	84.5 (75.0–97.0)	5	89.0 (86.0–100.0)	6

The patients were divided into quartiles according to their first measured TG values at the Lipid Clinic.
[a] Median, (minimum and maximum values)

4.4 Morbidity associated with hypertriglyceridemia

4.4.1 Coronary heart disease

In total, 11 participants had a medical history of CHD on referral, and 8 other patients experienced a coronary event during the study period (angina pectoris, myocardial infarction). Most of the patients with CHD were men (n=14). There was no significant difference between those with and without diagnosed CHD with respect to total-cholesterol, LDL-cholesterol, TG, apo A1, apo B, CRP or poorly controlled diabetes (glucose concentration, HbA1c) (table 22). The HDL-cholesterol concentration was significantly lower in patients with CHD (p=0.036). However, in a logistic regression this difference disappeared after adjusting for the other blood parameters listed in table 22, in addition to age, sex, smoking and hypertension.

Other risk factors, like smoking was more common in patients without CHD (54.3 %) compared to those with diagnosed CHD (42.1 %). However, there was no information about the patients smoking history before they started treatment at the Lipid Clinic. Regarding blood pressure, the median systolic blood pressure was 143.5 mmHg (95 % CI: 131.0–152.0) and 142.0 mmHg (95 % CI: 134.0–148.0), and the median diastolic blood pressure was 88.0 mmHg (95 % CI: 81.0–94.0) and 88.0

mmHg (95 % CI: 86.0–96.0) for those with and without diagnosed CHD respectively. The difference between the groups with respect to smoking, systolic and diastolic blood pressure was not statistically significant. However, the presence of hypertension was 89.5 % versus 45.7 % in those with and without diagnosed CHD respectively. This reflects a significantly higher presence of hypertension among the patients with CHD (p=0.003). Though, this condition was under medical treatment in nearly all these patients.

Ten of the patients with diagnosed CHD had a primary diagnosis of their hyperlipidemia. Seven of these patients had a familial combined hyperlipidemia, 2 patients a primary mixed hyperlipidemia and one patient a familial dysbetalipoproteinemia. Several of those with diagnosed CHD had other secondary diagnoses in addition. Nearly the same percentage of patients in both groups had the metabolic syndrome, while 53 % suffered from type 2 diabetes compared to 37 % of the patients with and without diagnosed CHD respectively.

Table 22. Blood parameters in patients with and without diagnosed CHD, n=65.

Blood measures at the start of treatment	No CHD			CHD			p-value
	n	Median	95 % CI	n	Median	95 % CI	
Frequency	46			19			
TG, mmol/L	45	11.9	(9.8–15.1)	19	14.1	(7.1–17.8)	0.628
Cholesterol, mmol/L	44	8.3	(6.9–9.3)	18	7.5	(6.4–10.6)	0.969
LDL, mmol/L	27	2.3	(1.7–3.5)	8	2.4	(0.7–5.5)	0.576
HDL, mmol/L	41	1.2	(1.0–1.3)	17	1.0	(0.7–1.1)	**0.036**
Glucose, mmol/L	38	5.8	(5.3–6.1)	13	6.0	(5.7–7.2)	0.163
HbA1c, %	31	5.6	(5.2–5.9)	13	5.7	(5.4–6.2)	0.597
Apo A1, g/L	25	1.2	(1.1–1.4)	10	1.2	(1.1–1.6)	0.815
Apo B, g/L	26	1.0	(0.9–1.2)	12	0.9	(0.7–1.2)	0.087
CRP, mg/L	31	2.1	(1.6–2.8)	11	2.6	(1.4–9.3)	0.146

4.4.2 Pancreatitis

Among the participants with pancreatitis (n=11), 27.3 % had a chronic type, 36.4 % had experienced an acute pancreatitis, while 36.4 % had experienced recurrent episodes of acute pancreatitis. The median TG value was highest in the group of patients with recurrent acute pancreatitis, and lowest in the group that never had

suffered from pancreatitis (table 23). There was a significant difference in TG values between the patients without experienced pancreatitis and patients who had suffered from either an acute, recurrent acute or chronic pancreatitis ($p<0.001$). However, there was no significant difference in TG values between the groups of patients with different types of pancreatitis.

Table 23. TG values in patients with and without pancreatitis, n=65.

	n	Median [a] mmol/L	95 % CI mmol/L	Minimum mmol/L	Maximum mmol/L	P-value
No pancreatitis	54	8.2	(7.5–10.2)	2.1	25.3	<**0.001** [b]
Pancreatitis	11	22.1	(11.9–39.8)	6.2	47.4	0.492 [c]
-acute	4	17.1	(11.9–25.4)	11.9	25.4	
-recurrent	4	29.5	(14.0–47.4)	14.0	47.4	
-chronic	3	22.6	(6.2–35.0)	6.2	35.0	

[a] To show a condensed view, the results in this table are based on the mean TG values to all the participants. Some patients had 2 TG measures, while others had several measures, and therefore we chose to estimate the mean TG value to the participants, and use these values to compare those with and without pancreatitis. The median in this table therefore refers to the median of all the mean TG values estimated for the participants.
[b] Comparison of mean TG values in patients with and without pancreatitis.
[c] Comparison of mean TG values in patients with acute, recurrent acute and chronic pancreatitis.

Only half of the study population (n=33) had measured the concentration of pancreas amylase one or several times while they were patients at the Lipid Clinic. Thirty percent of these patients had experienced pancreatitis. However, one of the patients with recurrent pancreatitis had never measured the concentration of pancreas amylase, although this patient came to regular controls at the Lipid Clinic for 6 years. Only 2 of the participants with reported pancreatitis had higher values of pancreas amylase than recommended. They both had a chronic pancreatitis, and one of them was an alcoholic. The median concentration of pancreas amylase was lowest in those without pancreatitis compared to those with a medical history of pancreatitis (table 24). However, there was no significant difference in the concentration of pancreas amylase between those with and without pancreatitis or between the patients with acute, recurrent acute and chronic pancreatitis.

Table 24. Pancreas amylase values in patients with and without pancreatitis, n=33.

	n	Median [a] U/L	95 % CI U/L	Minimum U/L	Maximum U/L	P-value
No pancreatitis	23	23.0	(17.0–24.5)	10.0	47.0	0.074 [b]
Pancreatitis	10	33.5	(15.0–47.5)	8.5	73.0	0.786 [c]
-acute	4	26.5	(19.0–40.0)	19.0	40.0	
-recurrent	3	39.0	(15.0–47.5)	15.0	47.5	
-chronic	3	47.3	(8.5–73.0)	8.5	73.0	

[a] To show a condensed view, the results in this table are based on the mean values of all the measures of pancreas amylase for each patient. Some patients had 2 measures, while others had several measures, and therefore we chose to estimate the mean value of pancreas amylase for all the participants, and use these values to compare those with and without pancreatitis. The median in this table will therefore refer to the median of all the mean values estimated for the participants.
[b] Comparison of mean values of pancreas amylase between those with and without pancreatitis.
[c] Comparison of mean values of pancreas amylase between the patients with acute, recurrent acute and chronic pancreatitis.

Four of the participants in the present study were diagnosed as alcoholics, and all of them had suffered from pancreatitis. One had experienced an episode of acute pancreatitis, another had suffered from recurrent episodes of acute pancreatitis, while two persons suffered from a chronic type. Although not diagnosed as an alcoholic, the alcohol intake might have been high in the other patients with pancreatitis as well. However, there was no significant difference in self-reported alcohol intake among those with and without pancreatitis in the present study (figure 15).

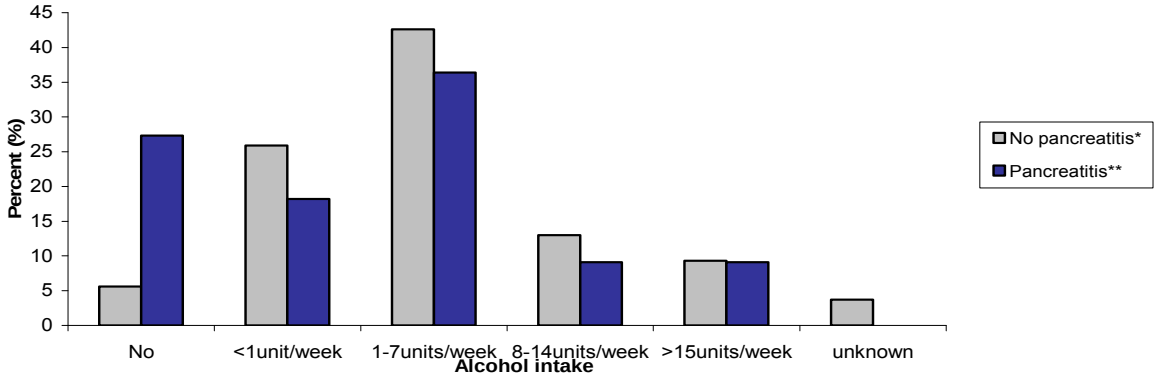

Figure 15. Mean alcohol intake among those with and without pancreatitis, n=65.

*No pancreatitis, n=54
**Pancreatitis, patients with a medical history of acute, recurrent acute or chronic pancreatitis, n=11

Six of the patients with pancreatitis had a primary hyperlipidemia, either type IIb or type V (table 25). One of the patients with type IIb hyperlipidemia was a woman trying to get pregnant. She had experienced several episodes of acute pancreatitis before she came to the Lipid Clinic, probably as a result of her hypertriglyceridemia. This female participant was followed up for approximately 6 years at the Lipid Clinic. During this period she had 4 spontaneous abortions and one abrupt pregnancy because of neural tube defect. Her primary hyperlipidemia probably made her especially susceptible for developing pancreatitis during pregnancy. However, this female participant did have two pregnancies with successful outcome, despite the development of acute pancreatitis in week 35 in one of these pregnancies.

Nearly all of the participants with pancreatitis had one or several secondary conditions in addition (table 26). The most common diagnosis in addition to the hyperlipidemia in patients with pancreatitis was type 2 diabetes, which was present in 54.5 % of the patients. However, the occurrence of type 2 diabetes was not significantly more present in those with pancreatitis compared to those without this condition.

Table 25. Primary diagnoses in addition to pancreatitis, n=11.

Type of pancreatitis	Type of primary hyperlipidemia [a]			
	Type IIb	Type III	Type IV	Type V
Acute/recurrent acute (n)	1	0	0	2
Chronic (n)	2	0	0	1
Total (n)	3	0	0	3

[a] The table does not include type I and type IIa hyperlipidemia because none of the participants in the present study were registered with these types.

Table 26. Secondary diagnoses in addition to pancreatitis, n=11.

Type of pancreatitis	Number of secondary diagnoses			
	0	1	2	≥3
Acute/recurrent acute (n)	2	1	3	2
Chronic (n)	0	0	0	3
Total (n)	2	1	3	5

5. Discussion

5.1 The method

5.1.1 Study design

The present study was retrospective, and this study design has both advantages and disadvantages. For instance, retrospective studies are often more easy and cheaper to perform since the data is already existing. However, this design might have a lower grade of scientific evidence than for instance prospective studies, partly because important data might be missing from medical records, and such data can be difficult to retrieve.

5.1.2 Study population

Patients with TG ≥10 mmol/L at the start of treatment were first meant to be eligible for the present study. However, to increase the number of participants in the study, the inclusion criteria were changed to patients who had TG ≥10 mmol/L at some point during their treatment time at the Lipid Clinic.

Informed consent was given by 58 % of the patients who fulfilled the inclusion criteria. There were several reasons for why the remaining did not want to participate. Some were not interested because they did not accomplish any benefits from the participation personally. Several patients said they would return the informed consent, but never did. One patient returned it without signature, but accompanied by a letter which stated that the patient was not satisfied with the public health service, and would therefore not help us. Others gave no specific reasons for why they did not want to participate. Fourteen patients were not reachable by phone. In addition, one consent was received in late April, but this patient was not included in the study because of the late response.

The majority of the participants were men. Abdominal obesity has been found to be significantly associated with hypertriglyceridemia, and this fat distribution is more

frequently seen in men compared to women (132). Despite of this, the few female participants in the present study had significantly higher TG values at the start of treatment compared to the male participants. However, the fact that there was a predominance of male participants indicates that severe hypertriglyceridemia might be a larger problem among men compared to women. This is also supported by another Norwegian study where 86 % of the individuals with TG values ≥10 mmol/L were men, and 14 % were women (Anja Schou Lindman, National Public Health Institution, personal communication).

5.1.3 Limitations

The study was not planned in advance before the included participants started treatment at the Lipid Clinic. This leads to several limitations. The notes in the medical records were written by different doctors and nutritionists, and the contents varied with respect to kind of information and how comprehensive the information was. Consequently, the medical records contained different amount and type of information for each patient, and also for the same patient at different consultations. The time between each consultation and the length of follow-up time at the Lipid Clinic was highly variable. Data on several variables included in this study were therefore lacking or incomplete for many of the participants. Waist circumference was one clinical measure there was little information about, and analyses concerning alteration in this parameter were therefore not performed. Lacking data is therefore a weakness in the present study.

Since nearly all the participants received both medical treatment and lifestyle recommendations while they were patients at the Lipid Clinic, it was difficult to estimate how great effects the respective treatment strategies had on the treatment outcome. Treatment results were therefore only possible to interpret as an effect of the two treatment strategies in combination.

The SmartDiet questionnaire existed in 2 different editions in the period 2002-2007. Some of the participants might therefore have used both editions. Only the total scores were taken into consideration, since it was difficult to compare scores on

specific questions for many of the participants. Unfortunately, the SmartDiet questionnaire is not available in the medical records, which contributes to difficulties in detecting specific changes in the diet to the patients. This highlights the importance of including this questionnaire in the medical records of the patients in the future. In addition, the newest edition of the SmartDiet questionnaire differs from the oldest in that it does not include the question regarding intake of sugar, snacks, and sweets in the total score. Patients who used both editions might therefore have made positive changes in their diet regarding intake of sugary food, without being detected and acknowledged in the present study.

Some patients did not take any clinical measurements, blood samples or did not answer the SmartDiet questionnaire following baseline. It was therefore impossible to consider the treatment effects for the whole study population with respect to changes in these parameters.

Information about TG and pancreas amylase values in the period before an episode of pancreatitis was difficult to obtain for many of the patients. Instead, the mean values for both TG and pancreas amylase were estimated for all the participants. However, these values do not represent the actual values before an episode of pancreatitis, and only give an impression of the patients with respect to these parameters.

The lack of data is also a problem which affects the statistical analyses and presentation of the results. When interpreting the figures and results in the present study, it is important to consider that the mean and median values for the parameters measured at different times are not related to exactly the same group of individuals.

The data material and analyses would probably have been more comprehensive and complementary if the study was planned before the included patients started treatment at the Lipid Clinic. It would also have been an advantage if the doctors/nutritionists followed the same standardised way of writing notes in the medical records.

5.2 The results

5.2.1 Diagnoses

Results from the present study showed that 43 % of the participants had a recorded primary diagnosis based on the Fredrickson classification of hyperlipidemias, while the rest only had secondary diagnoses that might explain their hyperlipidemia. This distribution is somewhat equal to the one found in a study conducted by Chait and Brunzell (133). They evaluated the role of familial and secondary factors in the etiology of severe hypertriglyceridemia in 54 patients. Familial factors were detected in 48 % of them, while only secondary factors were detected in the rest of the patients. However, these results characterized patients with even higher TG values (> 22.5 mmol/L) than in the present study.

Primary hypertriglyceridemia

In the present study, familial combined hyperlipidemia was found to be the most prevalent primary diagnosis which contributed to the hyperlipidemia in the participants. This correlates with other literature on this condition, which states that familial combined hyperlipidemia is considered as one of the most common genetic hyperlipidemias in the general population (26).

Nearly all of those with a primary diagnosis in the present study had one or several secondary diagnoses in addition. These secondary conditions might have contributed to even higher TG values, since the combination of familial and secondary causes of hypertriglyceridemia has been shown to interact and result in a marked elevation of TG (133). In addition, some of the primary diagnoses of hyperlipidemia need secondary factors for expression (30). In persons with a known genetic disorder it is therefore important to consider secondary conditions which also may contribute to the dyslipidemia.

Several similarities, like an increased concentration of VLDL, can make it difficult to distinguish properly between the different types of hyperlipidemias. In the present study, information about relatives with respect to lipid levels and CHD were

incomplete or lacking for several participants. This can result in erroneous or uncertain diagnosis, which has to be taken into consideration.

Secondary hypertriglyceridemia

Among the secondary diagnoses registered in the present study, nearly all of them can be related to the presence of hyperlipidemia. While most of the conditions might lead to elevations in TG values, some of the conditions might also have developed as a consequence of this lipid abnormality.

Nearly all of the participants (96.9 %) in the present study had one or several secondary diagnoses. The fact that the main part had ≥3 secondary conditions implies that these patients represent a group with considerably morbidity. The presence of at least one secondary diagnosis in addition to the hyperlipidemia has earlier been found to be very common. Ninety-four percent of the individuals in the study by Chait and Brunzell had potential secondary causes to their hypertriglyceridemia (133). Furthermore, dyslipidemia has earlier been reported to be developing more often secondary to different conditions rather than due to a primary genetic defect alone (25). The fact that patients with hypertriglyceridemia often have other conditions in addition substantiates the importance of these disorders in the development of hypertriglyceridemia, as well as in the treatment of hypertriglyceridemia.

There is no consensus about the use of a specific definition when diagnosing the metabolic syndrome (134). The definition from the International Diabetes Federation is more strict with respect to measures of the waist circumference. Information about this parameter was lacking for many of the patients in the present study, and the definition from the National Cholesterol Education Program was therefore more suitable. In addition, this definition might be favourable because some patients can develop multiple metabolic risk factors when the waist circumference is only marginally increased (6). The occurrence of the metabolic syndrome might be somewhat different in a study population depending on the chosen definition. However, an earlier study where the definitions from the International Diabetes Federation and the National Cholesterol Education Program were compared

concluded that both definitions identified approximately the same group of individuals (134). The metabolic syndrome was the most prevalent condition seen in the present study. This was not surprising since all the patients had elevated TG levels, and this lipid abnormality is an important component of the metabolic syndrome. Hypertriglyceridemia has earlier been detected in more than 3/4 of patients with the metabolic syndrome (135). The high percentage of patients with hypertension in the present study can also be seen in relation to the occurrence of the metabolic syndrome, since hypertension is another important component of this syndrome.

Type 2 diabetes was another common secondary diagnosis seen in the present study (41.5 %). This is consistent with earlier studies where untreated diabetes mellitus was the most common potential secondary cause of hypertriglyceridemia, either alone or in combination with another potential secondary cause (ethanol, estrogen) (133). The relation between hypertriglyceridemia and type 2 diabetes has been shown in earlier studies where fasting plasma TG and VLDL values were raised in both male and female diabetics (136). Results from a Norwegian study report that 1.6 % of men with TG >5 mmol/L and <10 mmol/L have diabetes, or a history of diabetes. In addition will 4.5 % of men with TG ≥10 mmol/L and <20 mmol/L, and 10.5 % of men with TG ≥20 mmol/L report the same thing. For women, the respective numbers are 4.3 %, 9.3 % and 33.3 % (Anja Schou Lindman, National Public Health Institution, personal communication). These results indicate that the presence of type 2 diabetes and hypertriglyceridemia increase in accordance with each other. However, this supports a strong link between the glucose and TG metabolism, which has been stated many times earlier as well (39).

Alcohol consumption has also been connected to elevated plasma TG levels (56). Only 6 % of the participants were diagnosed as alcoholics in the present study. In comparison, an earlier study found that ethanol was the secondary cause in 11 % of the individuals examined with hypertriglyceridemia (133). However, the alcohol consumption might have been high among the other participants in the present study,

although not diagnosed as alcoholics. Alcohol intake as a contributing factor to the hyperlipidemia in the participants might therefore have been underestimated.

The present study found a higher occurrence of some of the secondary conditions compared to earlier studies. For instance, hypothyroidism and kidney disease were present in 15 % and 6 % of the patients respectively, while hypothyroidism was only seen in 1.8 % and renal failure in 1.8 % of the individuals in an earlier study (133). However, the patients in that study had higher TG values (>22.5 mmol/L) compared to the patients in the present study. This can imply that hypothyroidism and kidney disease as contributing factors to hypertriglyceridemia usually does not lead to such extreme TG values as seen in that study. In addition, the present study registered patients with different kinds of kidney disease, not only patients with renal failure. This might also be a contributing factor to the higher occurrence of this condition in the present study.

When dividing the participants into quartiles according to their TG values, it became clear that the occurrence of different secondary conditions increased with higher TG values. The percentage of patients with ≥3 secondary diagnoses was high in all the groups, though it was clearly highest among the patients with TG values between 20 mmol/L and 30 mmol/L. This substantiates the fact that the presence of secondary diagnoses most likely had a strong effect on the TG values to the participants, and that several conditions in combination might have an additive or even a synergistic effect on the TG values.

5.2.2 Treatment of hypertriglyceridemia

Nearly all of the participants received medical treatment and they all got advice regarding diet and lifestyle when they were patients at the Lipid Clinic. It is difficult to say if the medication or the lifestyle recommendations had the greatest treatment effect. Most likely, the combination of both was responsible for the treatment results seen in the participants.

Medication

After the participants came to the Lipid Clinic, there was a significant increase in the use of medications which confirms that this is an important part of the treatment strategy in patients with hypertriglyceridemia at the Lipid Clinic. The majority of the patients used several medications in combination. At the end of treatment, the combination of a statin and Omacor was the most prevalent, and this combination might also have been very effective in these patients. Studies have shown that fish oil/statin combination in mixed hyperlipidemia has an additive effect, and might cause a greater TG reduction compared to fish oil or a statin used alone (137). In addition, 27.7 % of all the participants used a combination which included a statin and a fibrate. Studies have shown that patients with combined dyslipidemia, may benefit from such a combination (82). However, the drawback is that statins increase the risk of rhabdomyolysis, and this risk can be exacerbated with concomitant use of fibrates. For instance, gemfibrozil alters the statin metabolism and increases the plasma concentration of this medication (138). The Food and Drug Administration have reported several cases of severe myopathy and rhabdomyolysis with the concomitant use of lovastatin and gemfibrozil (139). There were no registered episodes of rhabdomyolysis among the patients who used a combination therapy in the present study. However, 4 of the participants complained about muscle and skeletal pain. This description was a bit vague, and could be a symptom of many conditions. None of these patients used a statin and a fibrate at the same time, so most likely this pain did not reflect a side effect of such a combination. Though, all four had used statins when they came to the Lipid Clinic, or during their treatment there. However, it is important to follow up patients who use statins, or a combination of statins and fibrates, with respect to adverse side effects.

Several patients used other medications as well that might have had an adverse effect on their TG level, for instance antihypertensive medications and resins. An earlier study compared one group of men who used diuretics with another group who did not use any antihypertensive medications (67). Results showed that the mean change in TG values was 0.12 mmol/L after one year of treatment with diuretics in doses up to 100 mg per day, while the mean change in TG values in the group who did not use

diuretics was -0.27 mmol/L. This difference between the two groups was significant. However, the effects of the diuretics on the TG values were small, and most likely the use of antihypertensive medications in the present study can not explain the high TG values in the patients, at least not as the only contributing factor. Resins are medications which usually have been restricted to patients with hypercholesterolemia, and advised not to be used in patients with hypertriglyceridemia (86). The 5 patients who used resins in the present study used other lipid-lowering medications in addition. Though, they did not use resins as a result of intolerance of other medications. Information regarding why these patients used resins in their treatment was not registered in their medical records. The impact this medication actually had on their lipid levels was difficult to estimate, among other things because of simultaneous use of other medications.

The treatment led to a significant reduction in median total-cholesterol and TG values following baseline. This reduction might indicate an effective medication at the Lipid Clinic, although the participants did not reach the recommended values. However, a common problem that must be considered is the compliance to treatment. It is difficult to measure compliance, but a review of patient adherence to treatment estimates that poor compliance is to be expected in 30-50 % of all patients, irrespective of disease, prognosis and setting (140). This problem was also seen in the present study, where some of the patients reported not to take their prescribed medications. Reasons were shortage of money, forgetfulness and lack of understanding of the importance of these medications. Poor compliance will have huge impacts on the treatment result, and better treatment effect would maybe have been accomplished if all the patients followed their prescribed treatment. To combat this problem it is important that doctors give thoroughly information to the patients to make sure they realise the importance of the treatment.

Lifestyle and diet

At the start of treatment, almost 50 % of the participants reported that they smoked on a daily basis. This result is consistent with another Norwegian study which reported that 58.5 % men and 59.2 % women with TG ≥10 mmol/L smoked daily (Anja Schou

Lindman, National Public Health Institution, personal communication). However, 24 % of the Norwegian population (≥16 years) reported of daily smoking in 2005 (141). This indicates that daily smoking is much more common among persons with hypertriglyceridemia compared to the population in general. This habit might be a strong contributing factor in the etiology of their hypertriglyceridemia.

Most of the patients reported a moderate alcohol intake. Many studies have shown an association between alcohol intake, even in moderate amounts, and lipid levels (142). However, these results are not entirely consistent. For instance, a Norwegian study showed that consumption of a glass of red wine daily had no significant effect on the TG concentration (143). Underreporting of alcohol intake might be a problem in the present study, and has to be taken into consideration.

A large part of the study population (43 %) reported that they seldom performed physical activity. This percentage of inactive patients was nearly 3 times higher than in the general population where inactivity is reported to be 15 % among individuals aged 25-66 years (141). Since the data were missing for 11 participants at the end of treatment, it was difficult to evaluate if there was an increase, a reduction or no change at all in this inactive lifestyle. However, this lifestyle change is especially essential since it is well known that exercise is one of the most important non-pharmacologic ways to reduce the level of TG (144). In a study by Wirth et al. they found that the TG concentration decreased with 25 % following endurance physical training in male participants with hypertriglyceridemia, compared to the control group with sedentary males with hypertriglyceridemia (145).

Regarding the diet, there was a strong trend indicating improvements in their reported diet following baseline. This might indicate an effect of the dietary counselling they received at the Lipid Clinic, though no information existed on potential counselling other places. The improvements in the diet might have been a contributing factor to the positive alterations seen in the lipid levels. Other studies also support the fact that diet modifications can have positive effects on the lipid levels. In a study by Man et al, dietary counselling in patients with hypertriglyceridemia was effective in reducing

the lipid levels (146). The TG and cholesterol levels were reduced with 31 % and 15 % respectively after 3 months.

Despite recommendations for lifestyle changes, including physical activity, alcohol intake and smoking, there were only small alterations following baseline in these parameters. The lack of significant changes might reflect that the patients did not understand the importance and effect these alterations might have on their lipid levels and health profile. Lifestyle changes are also hard to make, and patients need lots of motivation and encouragements to achieve these changes. This reflects the importance of regular follow-up consultations at for instance the Lipid Clinic or at their general practitioner. Although not significant, the accomplished alterations might still be of importance. Four of the participants did not use any medications during their time at the Lipid Clinic. Reasons for why these patients did not receive lipid-lowering medications were not documented. In addition, the changes in reported lifestyle habits and diet were small also for these patients. Still, their TG levels decreased following baseline with minimum 10.6 % and maximum 68.5 %. Though, this might indicate that even small changes with respect to lifestyle and diet can be of importance in the management of hypertriglyceridemia.

5.2.3 Baseline characteristics and effects of the treatment

Clinical measurements

Most participants were overweight (50 %) or obese (35.5 %) at the start of treatment at the Lipid Clinic. Results from another Norwegian study also showed that overweight was common in persons with hypertriglyceridemia. In this study the mean BMI for men with TG levels ≥10 mmol/L and <15 mmol/L was 29.1 kg/m^2, for those with TG levels ≥15 mmol/L and <20 mmol/L it was 30.4 kg/m^2, and when the TG levels were ≥20 mmol/L the mean BMI was 28.9 kg/m^2. The respective results for the female study population were 29.7 kg/m^2, 32.2 kg/m^2 and 27.1 kg/m^2 (Anja Schou Lindman, National Public Health Institution, personal communication). These results indicate that overweight and obesity are greater problems among patients with

hypertriglyceridemia than in the general population, where overweight was found in 34 %, and obesity was found in 9 % of the population (≥16 years) in 2005 (141).

In the same way as studies have shown a relation between overweight and hyperlipidemia, weight reduction has also shown to result in lower levels of TG (147). Unfortunately, there was no significant change in weight among the participants in the present study following baseline. Therefore, weight alteration was most likely not a contributing factor in the improvements of the lipid levels.

Blood parameters

It usually takes 3 months from referral until the patient gets a consultation at the Lipid Clinic. The significant reduction in TG levels at baseline compared to the referral values indicates that the patients who had very high TG levels (≥10 mmol/L) at referral (n=37) probably had made some lifestyle improvements before they came to the Lipid Clinic. In addition, some of these patients were also started on lipid-lowering medications by their general practitioner.

When considering all the included participants, there was a significant reduction in the concentration of total-cholesterol and TG following baseline. Both total-cholesterol and TG concentrations were still above the recommended values 3 years after baseline. However, complete normalization of TG values is reported elsewhere to rarely be achieved in patients with severe hypertriglyceridemia (79). Though, the lack of weight reduction, in addition to insufficient changes in lifestyle and diet habits might be explanatory factors for why the patients did not achieve even more profound reductions in their lipid levels. Although most of the patients used medications in their treatment, the type, dose and combination might not have been optimal in reducing their lipid values.

5.2.4 Morbidity associated with hypertriglyceridemia

Coronary heart disease

In the present study, 11 of the 65 participants had a medical history of CHD at referral. In addition, 8 other patients experienced a coronary event during the study

period. Hypertriglyceridemia is now recognised as an independent risk factor for CHD, and several epidemiological studies have shown an association between elevated plasma TG levels and increased CHD risk (113). However, other important risk factors were also present in many of the patients in the present study, for instance smoking, physical inactivity and an unhealthy diet. Most likely, the combination of several of these factors was responsible for the morbidity in these patients. Lifestyle changes and start-up with medications in the participants at the Lipid Clinic might have prevented future CHD in several of the participants.

Self-reported cardiac infarction has earlier been reported in 1.1 % of men with TG >5 mmol/L and <10 mmol/L, in 2.4 % of men with TG ≥10 mmol/L and <20 mmol/L and in 5.3 % of men with TG ≥20 mmol/L. All these men were in the age of 40-43 years (Anja Schou Lindman, National Public Health Institution, personal information). Although these results do not include women, the occurrence of CHD was much lower in that study compared to the present study. However, the present study included patients with all types of CHD, not only those with heart infarction. In addition, these two study populations might also differ with respect to the presence of other risk factors. Still, these results indicate that TG values and the occurrence of heart infarction/CHD increase in accordant with each other.

The most common primary hyperlipidemia in the patients with diagnosed CHD was familial combined hyperlipidemia. This finding is supported by other studies which consider this type as the most frequently genetic hyperlipidemia seen in patients affected by CHD (26). A prospective study of hypertriglyceridemic families demonstrated that first-degree relatives of probands in families with familial combined hyperlipidemia were at statistically significant increased risk of CVD mortality (70 %) compared to control subjects (148). Three other patients with CHD in the present study also suffered from primary hyperlipidemias associated with increased CHD risk.

Pancreatitis

In the present study, 11 of the 65 participants had experienced pancreatitis, and 8 of these had experienced one or several acute episodes during the study period. None of the patients in the present study were registered with a history of gallstone, which is the most important risk factor for developing pancreatitis (118). Alcohol is also reported as a risk factor in earlier studies (119), and 4 of the patients with pancreatitis in the present study were also alcoholics. In general, patients with experienced pancreatitis did not report a higher alcohol intake than patients without this condition. In fact, it seemed like the patients with experienced pancreatitis had a lower mean alcohol intake, although not significantly. This might indicate that the patients with pancreatitis had reduced their alcohol intake following an experienced episode of pancreatitis. It can also mean that a high alcohol intake was not the causative factor of the episodes in the present study. However, underreporting of alcohol intake is also a potential problem that has to be considered.

Hypertriglyceridemia has been reported in earlier studies to be the most common cause of acute pancreatitis not due to gallstone or alcohol (149). In the present study, the patients with pancreatitis had a median TG value of 22.1 mmol/L while the patients without experienced pancreatitis had a median TG value of 8.2 mmol/L. The fact that there was a significant difference in TG values between patients with and without pancreatitis might indicate that a high TG value could have been the causative factor in some of the patients with pancreatitis. In addition, acute and recurrent episodes of acute pancreatitis were the most common types of this condition in the present study. Earlier studies have concluded that pancreatitis due to hypertriglyceridemia usually presents either as one episode or recurrent episodes of acute pancreatitis, and rarely as chronic pancreatitis (122).

One of the patients with type IIb hyperlipidemia experienced several abortions, probably due to the development of acute pancreatitis in the pregnancies. This is reported to be an uncommon complication of pregnancy, but her pre-existing abnormality in the lipid metabolism may have been exacerbated during pregnancy and caused gestational hyperlipidemic pancreatitis (61).

All the participants with either acute or recurrent acute pancreatitis had one or several secondary diagnoses, with exception of 2 patients. Acquired forms of hypertriglyceridemia are reported not to cause a significantly elevation in TG concentration to be a risk factor for pancreatitis. However, in the presence of an underlying abnormality in the lipoprotein metabolism, the secondary conditions might increase the TG concentration to a level which might result in pancreatitis (122). Type 2 diabetes was the most common secondary condition in patients with pancreatitis in the present study. This might indicate that type 2 diabetes in patients with hypertriglyceridemia is an especially important secondary condition to consider, when evaluating the risk of pancreatitis. This is supported by an earlier cohort study which found that patients with type 2 diabetes had a 2.83-fold greater risk of pancreatitis compared to patients without diabetes (150).

6. Conclusion

The main results in the present study were:

(i) Twenty-eight patients had a registered primary diagnosis in their medical records which could explain their hyperlipidemia, and type IIb hyperlipoproteinemia (familial combined hyperlipidemia) was the most common type. More than 60 % of the participants had ≥3 diagnoses in addition to their hyperlipidemia. In the present study, the metabolic syndrome, hypertension and type 2 diabetes were the most common secondary conditions seen among the participants.

(ii) Nearly all the patients used medications in their treatment at the Lipid Clinic, and they all received recommendations for lifestyle improvements. There was a significantly increase in the use of medications after start of treatment at the Lipid Clinic. The lifestyle parameters did not change significantly over time compared with baseline.

(iii) Most of the participants were overweight or obese at the start of treatment at the Lipid Clinic. Regarding blood parameters, only total-cholesterol and TG values were elevated above the recommended at baseline. The treatment had a positive effect on the lipid levels and the blood pressure to the participants. However, the treatment had no significant effect on their body weight.

(iv) Among all the participants, 29 % were diagnosed with CHD and 17 % had experienced one or several episodes of acute pancreatitis, or had a chronic pancreatitis.

Patients with hypertriglyceridemia represent a group which are affected by morbidity in a large degree. A future challenge is to identify untreated patients with hypertriglyceridemia and initiate an effective treatment to reduce their risk for complications like CHD and acute pancreatitis.

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8. Appendix

Appendix 1. Approval from the Regional Committee for Medical Research Ethics

Overlege dr.med. Kjetil Retterstøl
Lipidklinikken
Rikshsopitalet-Radiumhospitalet HF

Regional komité for medisinsk og helsefaglig forskningsetikk Sør-Øst A (REK Sør-Øst A)
Postboks 1130 Blindern
NO-0318 Oslo

Telefon: 22 84 46 66
Telefaks: 22 85 05 90
E-post: jorgen.hardang@medisin.uio.no
Nettadresse: www.etikkom.no

Dato: 30.06.08
Deres ref.:
Vår ref.: S-08337a, saksnummer: 2008/8674

S-08337a Alvorlig hypertriglyseridemi: Årsaker og behandling [6.2008.1118]

Vi viser til brev datert 18.6.08 med informasjonsskriv med samtykkeerklæring vedlagt.

Komiteen har ingen merknader til revidert informasjonsskriv med samtykkeerklæring.

Komiteen godkjenner at prosjektet gjennomføres.

Med vennlig hilsen

Kristian Hagestad
Fylkeslege cand.med., spes. i samf.med
Leder

Jørgen Hardang
Komitésekretær

Appendix 2. Approval from the Data Inspectorate

IT-avdelingen

NOTAT

Besøksadr: Forskningsveien 2 B, Oslo
Postadr: Rikshospitalet HF, 0027 Oslo
Sentralbord: 23 07 00 00
Direktelinje: 23 07 50 34
Epost: firmapost@rikshospitalet.no
personvern@rikshospitalet.no

Til: Kjetil Retterstøl, overlege, Lipidklinikken

Kopi: Ingvild Veseth, student, UiO

Fra: Aksel Sogstad, personvernombud

Saksbehandler:

Dato: 13. august 2008

Offentlighet: Ikke unntatt offentlighet

Sak: 08/3914: Tilrådning av forskningsstudie unntatt konsesjon

Tilrådning til innsamling og databehandling av personopplysninger i forskningsstudien "Alvorlig hypertriglyseridemi: Årsaker og behandling"

Personvernombudet har vurdert det til at den planlagte databehandlingen av personopplysninger tilfredsstiller forutsetningene for melding gitt i personopplysningsforskriften § 7-27 og derfor er unntatt konsesjon. Personvernombudet har myndighet til å foreta denne avgjørelsen på vegne av Datatilsynet.

Det tilrås at prosjektet igangsettes med følgende betingelser:

- Data lagres avidentifisert på en av sykehusets forskningsservere (O:Forskning, Forskernett eller MedInsight). Annen lagringsform forutsetter gjennomføring av en risikovurdering som må godkjennes av personvernombud. Se referanser.
- Kryssliste som kobler avidentifiserte data med personopplysninger lagres separat på prosjektleders avlåste kontor.
- Data slettes eller anonymiseres (ved at krysslisten slettes) senest ved prosjektslutt 31.12.09
- Studiet må vurderes og tilrås av Regional komité for medisinsk forskningsetikk (REK), og eventuelle merknader må følges. Kopi av tilrådning fra personvernombudet vedlegges søknaden til REK.
- Informasjonsskrivet endres slik at:
    - det påføres en logo
    - at det kommer fram at Rikshospitalet er ansvarlig for gjennomføring av studien
    - at den registrerte har rett til innsyn, retting og sletting av opplysninger

Kontaktperson for prosjektet skal hvert tredje år sende personvernombudet ny melding som bekrefter at databehandlingen skjer i overensstemmelse med opprinnelig formål og helseregisterlovens regler. Hvis formålet eller databehandlingen endres må personvernombudet informeres om dette. Studien er registrert i Rikshospitalets offentlig tilgjengelig database over forsknings- og kvalitetsstudier http://forpro.

Med vennlig hilsen

(sign.)
Aksel Sogstad
Personvernombud
Rikshospitalet HF

Referanser

1-ADM.2.6.1 Risikovurdering av informasjonssikkerhet

1-FOR.4.05 Lagring, arkivering og sletting av helse- og personopplysninger i forskningsstudier og kvalitetssikring

1-FOR.4.09 Utforming av samtykke og informasjonsskriv ved ekstern og intern databehandlingsansvarlig

1-FOR.11.0.2 Mal for forespørsel om deltakelse i forskningsprosjekt

Appendix 3. Informed consent

Medisinsk klinikk
Lipidklinikken
RIKSHOSPITALET

Besøksadr: Forskningsveien 2 B, Oslo
Postadr: Rikshospitalet HF, 0027 Oslo
Sentralbord: 23 07 00 00
E-post: firmapost@rikshospitalet.no

Dato:

Forespørsel om deltakelse i forskningsprosjekt
Pasientinformasjon og samtykkeerklæring

Forespørsel om å delta i klinisk studie
Dette er et spørsmål til deg om å delta i studien "Alvorlig hypertriglyseridemi: Årsaker og behandling". Før du bestemmer deg for om du vil delta bør du lese denne informasjonen nøye. Kontakt gjerne en av de ansvarlige for studien dersom du har noen spørsmål.

Hva skjer hvis jeg velger å delta i studien?
Studien baserer seg på å samle data fra pasientjournaler. Hvis du velger å delta betyr det at du gir tillatelse til at din pasientjournal leses for å finne fellesnevnere for pasienter med hypertriglyseridemi. Studien innebærer ikke noen ekstra undersøkelser eller oppmøte på Lipidklinikken.

Bakgrunn og hensikt
Studien ønsker å kartlegge de mest vanlige primære og sekundære underliggende årsakene til alvorlig hypertriglyseridemi og hvilken type behandling som gis til pasienter med hypertriglyseridemi som behandles ved Lipidklinikken, Rikshospitalet- Radiumhospitalet.
Det er i tillegg ønskelig å kartlegge hvilken effekt den medikamentelle behandlingen og kostbehandlingen har på hypertriglyseridemi. Studien vil pågå fra høsten 2008 til høsten 2009.

Hva innebærer studien?
Studien innebærer en gjennomgang og analyse av pasientjournaler til alle pasienter med diagnosen alvorlig hypertriglyseridemi som har fått behandling ved Lipidklinikken i perioden 2002-2007. Det er i tillegg ønskelig å sende et spørreskjema til deltagerne via posten for å samle ytterligere informasjon underveis i studien. Det er opp til hver enkelt om de ønsker å svare på dette spørreskjemaet.

Hva skjer med informasjonen om deg?
All informasjon som innhentes fra pasientjournalen din i forbindelse med denne studien vil bli behandlet konfidensielt. Informasjon og opplysninger vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger gjennom en navneliste. Det er kun autorisert personell ved Lipidklinikken som er knyttet til prosjektet som har adgang til navnelisten og som kan finne tilbake til deg. Du har rett til innsyn, retting og sletting av opplysninger. All informasjon og opplysninger som hentes ut fra pasientjournalene vil bli bli slettet innen slutten av 2009. Det vil ikke være mulig å

identifisere deg i resultatene av studien når disse publiseres.

Hvem vi ønsker å inkludere:
Kvinner og menn over 18 år med diagnosen alvorlig hypertriglyseridemi (fastende triglyseridnivå $\geq$10 mmol/L).

Fordeler og ulemper med å delta i prosjektet:

Fordeler:
Du bidrar til å øke kunnskapen om hvilke faktorer og forhold som øker risikoen for alvorlig hypertriglyseridemi, og hvilken behandling som er mest effektiv i forhold til denne diagnosen.

Ulemper:
Det er ingen kjente ulemper eller ubehag ved å delta i denne studien.

Frivillig deltakelse
Deltakelse er frivillig. Du kan når som helst trekke ditt samtykke til å være med i denne studien uten å oppgi grunn for dette. Dersom du velger å ikke delta, eller å trekke deg underveis, vil dette ikke ha noen betydning for din videre oppfølging og behandling ved Lipidklinikken. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side og returnerer den i den vedlagte frankerte svarkonvolutten.

Andre viktige opplysninger
Etter gjeldende regler er studien blitt vurdert av Regional komité for medisinsk forskningsetikk, og meldt til Personvernombudet for forskning.
Ansvarhavende for prosjektet er masterstudent i ernæring Ingvild Veseth (e-mail: ingvild.veseth@studmed.uio.no, tlf: 99635459), og overlege Kjetil Retterstøl, Lipidklinikken, Rikshospitalet (e-mail: kjetil.retterstol@rikshospitalet.no).

SAMTYKKEERKLÆRING

Forespørsel om å delta i studien: " Alvorlig hypertriglyseridemi: Årsaker og behandling"

Jeg har lest informasjonen ovenfor og vil delta i studien. Jeg er inneforstått med at jeg når som helst kan trekke meg uten å oppgi grunn, og uten at det får følger for min ordinære behandling.

Dato: _____ Navn på prosjektdeltager i blokkbokstaver _____ Signatur

Jeg er villig til å motta og svare på et spørreskjema (sett ring rundt): JA NEI

Dato: _____ Navn på prosjektansvarlig i blokkbokstaver _____ Signatur

Appendix 4: SmartDiet questionnaire

De gode rådene finner du her

Mettet fett er kolesteroløkende. Reduser derfor inntaket av matvarer med mye mettet fett. Velg i stedet matvarer med mye umettet fett som kan senke kolesterolet.

Drikk mager melk, 1/2 liter skummet, søt eller sur, daglig. Dersom du ikke drikker melk daglig, kan det føre til et for lavt inntak av kalsium.

Alle fløte- og rømmetyper inneholder mye mettet fett og anbefales ikke i hverdagskostholdet. Cultura, skummet kultur, lettmelk, ekstra lettmelk, skummet melk, yoghurt og Kesam (1% fett) kan brukes i matlaging, til sauser og dressing.

Ost er en kilde til store mengder mettet fett. Velg lettere eller mager ost (ost med mindre enn 10 % fett) til hverdags. Ikke bruk lettere ost som pålegg på mer enn en tredel av dagens brødskiver. Vær også oppmerksom på mengde og type ost du bruker i matlagingen.

Fett kjøtt er også en kilde til store mengder mettet fett. Velg kjøtt med mindre enn 10 % fett både som middagsmat og som pålegg. Skjær bort alt synlig fett, og spis minst mulig oppblandede kjøttprodukter. Velg for eksempel karbonadedeig eller kylling-/ svinekjøttdeig fremfor kjøttdeig. Fjern skinnet på kylling, kalkun og annet fjærkre. Velg skinkeprodukter fremfor salami, fårepølse og lignende.

Spis alle typer fisk til middag flere ganger i uken. Fet fisk som makrell, sild, laks og ørret inneholder umettet fett (omega-3) og er derfor spesielt gunstig. Spis fisk som pålegg daglig. Ta i tillegg 1 skje tran, eventuelt 2 fiskeoljekapsler, daglig året rundt.

Bruk gjerne majonespålegg daglig, men i moderate mengder.
De fleste majonesprodukter inneholder mye olje og derfor mye fett (og kalorier!), men fettet er umettet og derfor gunstig.

Myk plantemargarin er en god kilde til umettet fett. Velg typer med mer enn
70 % umettet fett. Velg gjerne margarin med plantesteroler. Plantesteroler er gunstig for kolesterolet.

Bruk gjerne olje, flytende eller myk plantemargarin i matlagingen (velg typer med mer enn 70 % umettet fett). Spis mindre stekt mat. Velg heller kokt eller ovnsstekt mat, da vil behovet for fett i matlagingen reduseres.

Grove kornprodukter er viktig i hverdagskostholdet. Spis mye av alle sorter fiberrike kornprodukter. Havre er spesielt gunstig og bør brukes regelmessig. Brødet bør inneholde mer enn 6 gram fiber pr 100 g brød. Se også etter Brødskala'n på emballasjen.

Husk "5-om-dagen". Spis minst to porsjoner frukt eller bær hver dag.
Fyll halve middagstallerkenen med grønnsaker, både rå og lettkokte. Spis grønnsaker som mellommåltid, som pålegg og som pynt på pålegget. Vær raus med porsjonene.
Erter, bønner og linser kan med fordel spises ofte.

En porsjon poteter, ris eller pasta er et fint tilbehør til middagen daglig.

Bruk minst mulig sukker, sukkerholdig mat og drikke, som kjeks, kaker, is, søtt pålegg, sukkergodt, sjokolade, juice, nektar, saft og brus. Disse produktene gir ingen næringsstoffer men kan bidra til økt vekt. Sukker kan også øke triglyseridene.

Nøtter og mandler inneholder gunstig umettet fett, men er veldig kaloririke. Bruk det derfor gjerne, men i begrenset mengde. Kokosnøtten og Chillinøttene inneholder mye mettet fett og bør derfor unngås.

Kaffebønnen inneholder fettstoffer som øker kolesterolet. Velg derfor pulverkaffe (inneholder ikke fett) eller kaffe som blir filtrert. Filteret fjerner det meste av fettstoffene. Husk at kaffe tilsatt melk (for eksempel Cafe latte, cappucino) kan være en kilde til mettet fett avhengig av melketypen som brukes og mengde kaffe som drikkes.

Alkohol inneholder mye kalorier og kan derfor føre til vektøkning. Alkohol kan også øke triglyseridene.

Eggeplommen inneholder mye kolesterol. Begrens inntaket til to eggeplommer per uke. Den største kilden til kolesterol i kostholdet er likevel matvarer rike på mettet fett.

Spørreskjemaet vil ikke nødvendigvis gi et komplett bilde av ditt kosthold. Du kan få mer informasjon om kostholdet i heftet "Kostbehandling ved høye blodlipider hos voksne" (Lipidklinikken 2006).

Spørsmål 1-13 med unntak av spørsmål 10 er evaluert i forhold til veid kostholdsregistrering.

Kilde: Svilaas A, Ström EC, Svilaas T, Borgejordet Å, Thoresen M, Ose L. SmartDietTM, a health educational tool. Reproducibility and validity of a short food questionnaire for assessment of dietary habits. Nutr Metab Cardiovasc Dis 2002; 12: 60-70. Skjemaet er revidert i 2007.

64521 Wero RS, Porsgrunn

SmartDiet™

25 spørsmål om ditt kosthold og din livsstil

Les spørsmålene og de angitte svarmulighetene nøye!

Sett kryss ved det svaret som passer best med det du *vanligvis* spiser.

Kommentarer:

Antall poeng: _____

Kostholdsvurdering

24 poeng eller mindre:	Du bør forbedre kostholdet ditt på mange punkter, for å gjøre det mer helse- og hjertevennlig.
25-30 poeng:	Du kan forbedre kostholdet ditt på en del punkter, slik at det blir mer helse- og hjertevennlig.
31 poeng eller mer:	Du har sunne kostholdsvaner.

Navn: .....

Fødselsdato: ..... Dato for besvarelsen: .....

Navn på fastlege: .....

Adresse til fastlege: .....

1. Melk (sur/søt) og yoghurt

Hvor mange små beger med yoghurt (ca 1 dl) spiser du i løpet av en uke? Antall:.....

Hvor mange glass melk drikker/bruker du daglig? Antall:.....

Hvilken type melk bruker du oftest som drikke, i matlagingen, på gryn, i grøt, i dessert, i kaffe/te ol.?

Helmelk • Kulturmelk • Kefir • Kaffemelk 5 % fett .....
Lettmelk • Cultura • Biola (syrnet lettmelk) • Ekstra Lett melk .....
Skummet melk • Skummet kulturmelk • Biola bærdrikk (0,1 % fett) .....
Drikker/bruker mindre enn 1 liter melk i uken eller aldri .....

2. Fløte, rømme og lignende.

Hvilken type bruker du oftest i matlagingen, i dressing, i dip, i kaker, i kaffe/te ol.?

Kremfløte • Créme Fraiche • Seterrømme • Pisket krem .....
Matfløte • Lettrømme .....
Kaffefløte • Ekstra lettrømme • Vikingmelk • Kesam • Matyoghurt. .....
Bruker ikke ukentlig eller bruker aldri .....

3. Ost på brødmaten, i matlaging, på pizza o.l.

Hvor mye ost som pålegg, regnet i osteskiver eller i spiseskjeer (for smørbar ost) spiser du daglig? Antall:.....

Til hvor mange middager per uke bruker du ost? (eks. pizza, taco, gratinering, lasagne, i saus, i salat ol.) Antall:.....

Hvilken type ost bruker du oftest?

Hvitost • Nøkkelost • Gudbrandsdalsost (G35) • Ekte geitost • Fløtemysost • Edamer • Gräddost • "Dessert oster" • Smørbare fete oster • Mozzarella • Fetaost • Revet pizza-/pastaost • Taffelost • Burgerost • Snøfrisk • Parmesan .....
Lettere hvitost • Lettere nøkkelost • Lettere fløtemysost • Lettere Gudbrandsdalsost • Lettere smørbare oster • Mozzarella • Fetaost • Prim med vaniljesmak .....
Ost med raps og solsikkeolje • Cottage cheese • Gamalost • Pultost • Mager mysost • Prim • Mager prim .....
Jeg bruker ost en gang i uken eller aldri .....

4. Kjøttpålegg

Hvilken type kjøttpålegg bruker du oftest?

Leverpostei • Salami • Lett salami • Servelat • Fårepølse • Stabburpølse • Morrpølse • Haugpølse • Reinsdyrpølse • Falukorv • Fleskepølse • Sylte • Lammerull • Paté • Fenalår .....
Kokt/røkt skinke • Hamburgerrygg • Krydderskinke Pastramiskinke • Roastbiff • Bankekjøtt • Kylling- og kalkunpålegg • Lett servelat • Kalverull • Spekeskinke uten fettrand • oljebaserte posteier (Vita/Mills, Delikat, Gilde) eller mager leverpostei .....
Bruker ikke kjøttpålegg ukentlig eller bruker aldri .....

5. Kjøtt til middag

Hvilken type bruker du oftest?

Familiedeig • Medisterdeig • Grillpølse • Wienerpølse • Kjøttpølse • Medisterpølse • Knakkpølse • Nakkekoteletter med fettrand • Lammekoteletter • Medisterkake • Wienerschnitzel • Bacon • Flesk • Grillben • Fårekjøtt .....
Kjøttdeig (okse, lam) • Kyllingpølse • Lettpølse • Kjøpte karbonader • Hamburger • Kebabkjøtt • Kjøttkaker • Kjøttpudding • Kamkoteletter med fettrand • Nakkekoteletter uten fettrand • Kylling, kalkun og høne med skinn • Bayonneskinke med fettrand • Hamburgerrygg med fettrand .....
Karbonadedeig • Kjøttdeig (svin, kylling) • Biff • Filet (kylling, svin, okse, lam) • Viltkjøtt • Stek uten fettrand • Bogskinke • Kamkoteletter uten fettrand • Kjøtt uten synlig fett • Kylling, kalkun og høne uten skinn .....
Jeg spiser ikke kjøtt ukentlig eller aldri .....

6. Fiskepålegg

Hvor ofte har du fiskepålegg på brødmaten?

Eksempler: Laks • Makrell • Sild • Sardiner • Brisling • Tunfisk • Reker • Krabbe • Crab-sticks • Fiskepudding • Fiskekaker m.fl

På inntil 1 brødskive i uken, eller aldri .....
På 2-4 brødskiver i uken .....
På 5 eller flere brødskiver per uke .....

7. Fisk til middag

Hvor mange ganger i uken spiser du fisk, fiskemat og/eller fiskeretter?

Inntil en gang i uken eller aldri .....
2 ganger i uken .....
3 eller flere ganger i uken .....

Til hvor mange av disse middagene spiser du fet fisk ukentlig?

Antall:.....
Med fet fisk menes f.eks. ørret, laks, makrell, kveite, sild.

8. Majones, remulade og kaviar

Hvor ofte bruker du majonesprodukter, remulade og/eller kaviar på brødmaten?

Eksempler: Majones • Rekesalat • Italiensk salat • Crab-stick salat • Skagensalat • Frokostsalat • Remulade • Kaviar/kaviarmix mfl.

På inntil 1 brødskive i uken, eller aldri .....
På 2-7 brødskiver i uken .....
På 8 eller flere brødskiver per uke .....

9. Smør eller margarin på brødmaten

Hvilken type bruker du oftest?

Alle typer smør • Smøregod • Bremyk • Brelett • Melange margarin • Per margarin • Soft margarin uten salt og melk • Letta .....
Soft Flora • Soft Light • Soya margarin • Soya lett margarin • Oliven margarin • Olivero • Solsikke margarin • Soft Ekstra .....
Vita • Vita lett • Vita Pro-aktiv • Becel Pro-activ • Münsterland Organic Margarin .....
Bruker vanligvis ikke smør eller margarin på brødmaten .....

10. Bruker du et produkt som inneholder plantesteroler?

Bruker du produkter som inneholder plantesteroler?
Eksempler: Vita pro-aktiv • Becel pro-aktiv • yoghurt shot ◯ ja ◯ nei

11. Fett i matlagingen

Hvilken type fett bruker du oftest til steking, baking, i saus, som dressing ol.?

Alle typer smør • Bremyk • Smøregod • Melange margarin • Per margarin • Soft Flora stekemargarin • Soya stekemargarin .....
Soft Flora • Soya margarin • Solsikke margarin • Oliven margarin • Olivero • Soft Ekstra .....
Olje • Flytende margarin • Vita .....
Bruker vanligvis ikke fett i matlagingen .....

12. Brød, knekkebrød og andre kornprodukter

Hvor mange skiver brød, rundstykker eller knekkebrød spiser du daglig? Antall:.....

Hvor mange porsjoner havregrøt, kornblanding eller andre typer frokost-blandinger spiser du daglig? Antall:.....

Hvor grove kornvarer bruker du?

Spiser oftest brød, knekkebrød, kornblandinger og lignende med lite fiber, dvs fint mel er hovedingrediensen og matvaren har mindre enn 50 % grovhet.
Eksempler: Kneippbrød • Loff • Fine rundstykker • Baguetter • Ciabatta • Lyst knekkebrød • Riskaker • Puffet ris • Cornflakes • Havrenøtter • Frokostkorn med (sjokolade, honning, sukker) m.fl. .....
Spiser oftest brød, knekkebrød, kornblandinger og lignende med mye fiber, dvs sammalt mel er hovedingrediens og matvaren har mer enn 50 % grovhet.
Eksempler: Rugbrød • Pumpernikkel • Mørke knekkebrød • Rugsprø • Fiberrik • Havregryn • Weetabix, Havrefras • Shredded wheat m.fl. .....
Spiser ikke brød, knekkebrød, eller andre kornprodukter .....

13. Grønnsaker, frukt og bær

Hvor mange porsjoner grønnsaker, frukt og bær spiser du daglig?

1 porsjon=150g som tilsvarer ca 2 gulrøtter eller ca 1 1/2 eple

Mindre enn 2 porsjoner (< 300g) .....
2-4 porsjoner (300-600g) .....
4 porsjoner eller mer (≥ 600g) .....

Hvor mange av disse porsjonene er grønnsaker? Antall:.....

Totalt antall poeng: _____

14. Belgvekster

Spiser du belgvekster ukentlig? ◯ Ja ◯ Nei

Eksempel: hvite tomatbønner, brune bønner, kikerter, linser, erter, sukkererter.

15. Potet, ris og pasta

Hvor mange porsjoner poteter, ris og/eller pasta spiser du daglig?

En porsjon tilsvarer 2 poteter eller 1 dl kokt ris eller 1 dl kokt pasta/spagetti

◯ Spiser ikke ◯ 0-1 porsjon ◯ 2 porsjoner ◯ 3 porsjoner eller fler

16. Sukker, søtt pålegg, søt drikke, kaker, kjeks og annet snacks

Bruker du mer enn 1,5 dl søt drikke daglig? ◯ Ja ◯ Nei

Eksempel: Saft • Brus • Fruktjuice • Nektar

Spiser du sjokolade ukentlig? ◯ Ja ◯ Nei
Spiser du fløteis ukentlig? ◯ Ja ◯ Nei
Spiser du annet snacks som potetgull, ostepop, baconcrisp, tortilla chips o.l. ukentlig? ◯ Ja ◯ Nei
Spiser du kake eller kjeks ukentlig? ◯ Ja ◯ Nei
Spiser du smågodt, seigmenn eller annet sukkergodt ukentlig? ◯ Ja ◯ Nei

17. Nøtter og mandler

Spiser du nøtter/mandler ukentlig? ◯ Ja ◯ Nei

18. Kaffe

Drikker du kaffe? ◯ Ja ◯ Nei

Hvis ja, hvilken type?:.....

F.eks. cappucino, café latte, kokekaffe, traktekaffe, pulverkaffe

19. Alkohol

Drikker du alkohol? ◯ Ja ◯ Nei

Hvis ja, hvor mange enheter drikker du til sammen hver uke?

◯ Mindre enn 1 ◯ 1-7 ◯ 8-14 ◯ Mer enn 15

1 enhet =
1 glass vin (125 ml)
1 glass øl (0.33 l)
4 cl brennevin

20. Egg

Hvor mange egg, inkludert i matlaging, spiser du per uke? Antall.....

1. Måltidsmønster

Hvor mange måltider spiser du daglig? ◯ 1 til 2 måltider ◯ 3 måltider ◯ 4 måltider ◯ 5 eller flere måltider

2. Høyde og vekt

Høyde:..... cm Vekt:..... kg

Jeg ønsker å gå ned i vekt ◯ Nei ◯ Ja

Hvis ja, hvor mange kilo ønsker du å gå ned i vekt? ..... kg

3. Røyk/snus

Røyker du? ◯ Nei ◯ Ja ◯ Ja, selskapsrøyker

Hvis ja, hvor mange sigaretter/piper røyker du per dag? Antall .....

Snuser du? ◯ Nei ◯ Ja

Hvis ja, hvor mange porsjoner snuser du per dag? Antall .....

4. Mosjon

Hvor ofte mosjonerer du i minst 30 minutter?

Rask gange, løping, skigåing, svømming, sykling etc.

◯ Sjeldnere enn 1 gang per uke eller aldri
◯ 1 til 2 ganger per uke ◯ 3 eller flere ganger per uke

5. Kosttilskudd

Bruker du kosttilskudd? ◯ Nei ◯ Tran ◯ Fiskeoljekapsler/omega3-kapsler ◯ Multivitaminpreparat ◯ Annet:.....